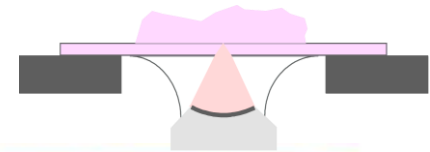
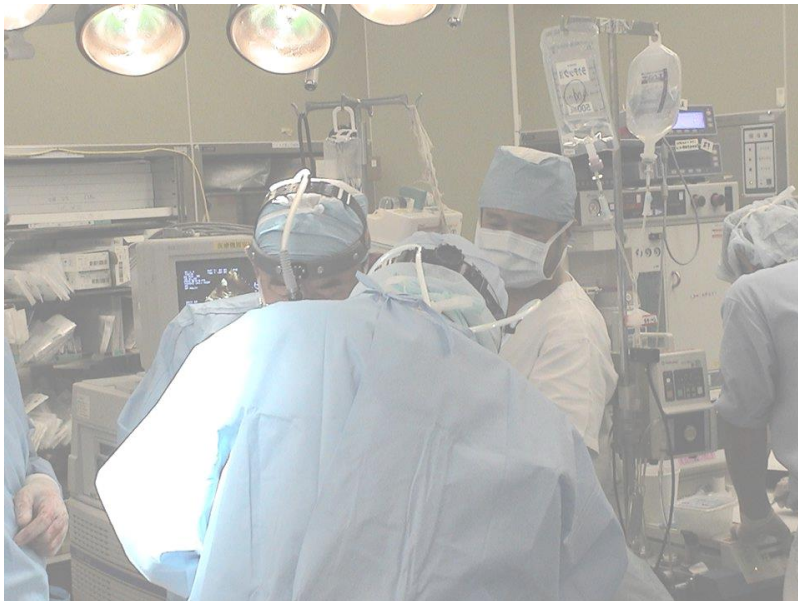
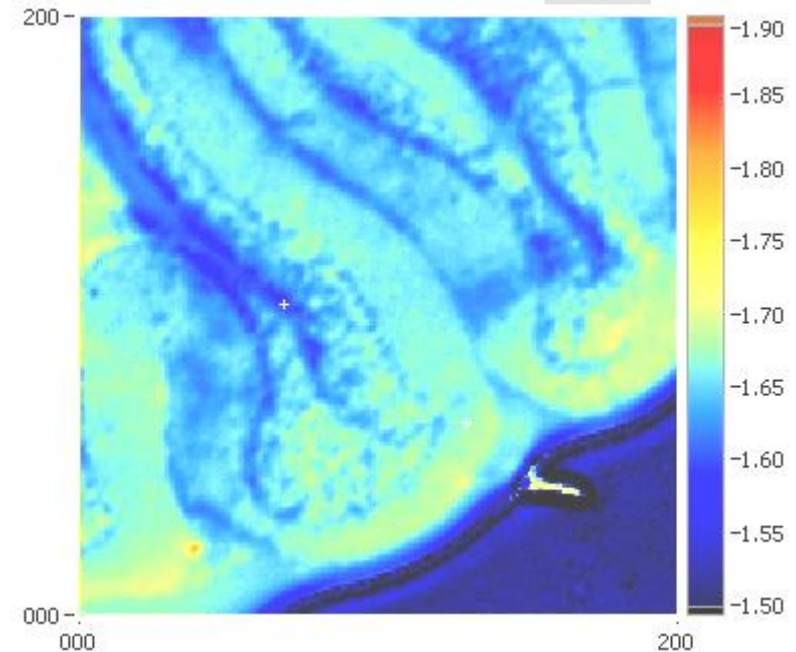


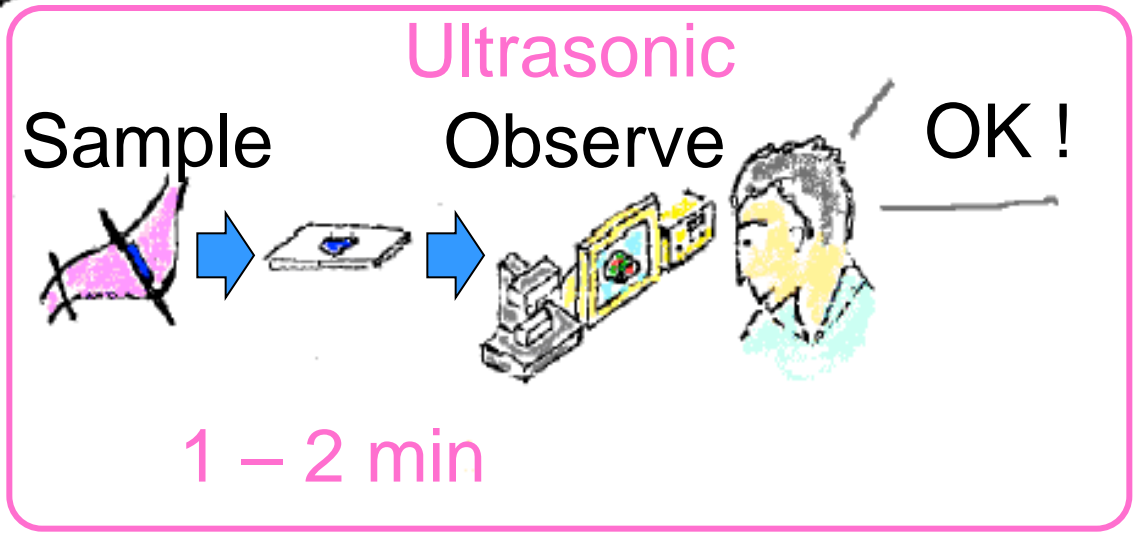
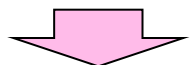
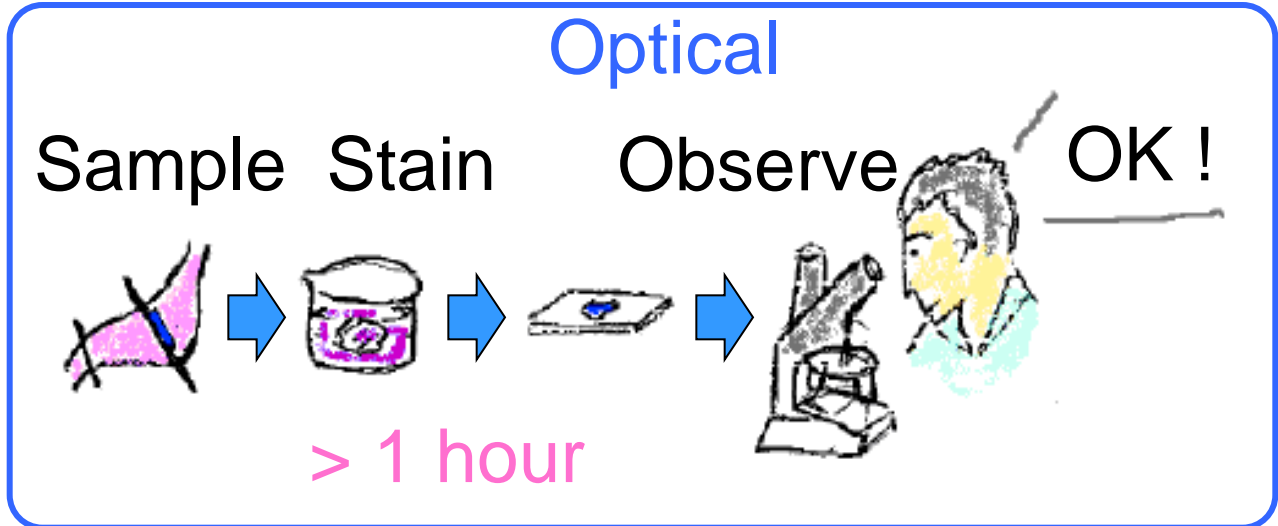
医学生物学用超音波顕微鏡



Naohiro Hozumi
Toyohashi University of Technology,
JAPAN
hozumi@icceed.tut.ac.jp



A clinical need.



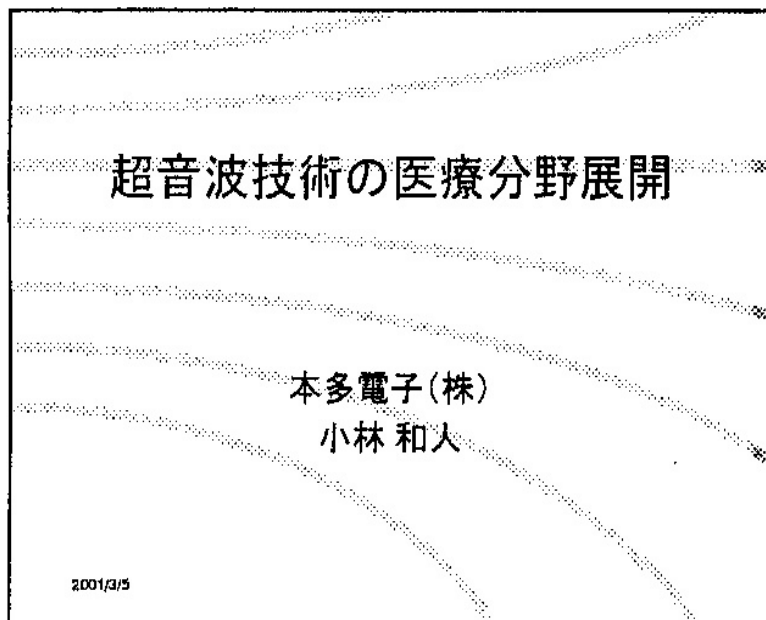
パネルディスカッションがあった。

医療機器開発に向けた医・工連携の構築と
情報化医療機器とは

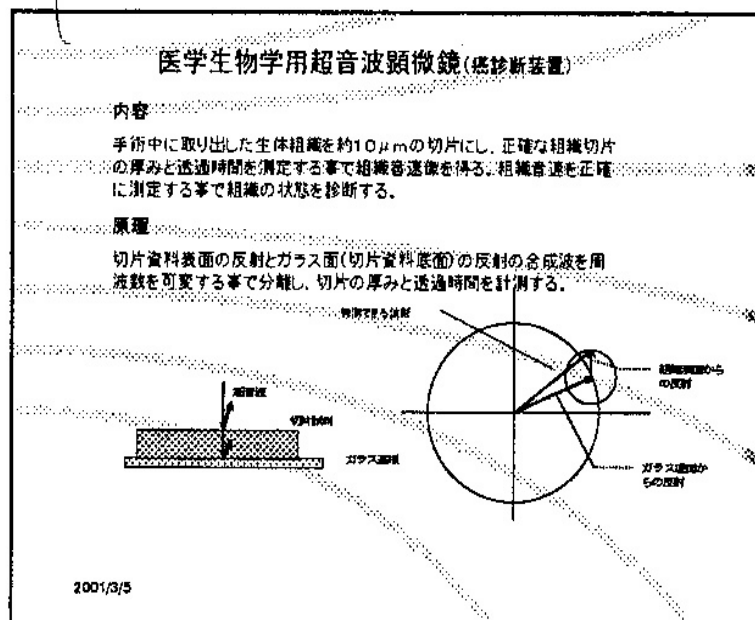
パネラー 小林和人氏(本多電子(株))

原いかり
音速が変化するので、波の折る

当時の配布資料



(2001年3月5日)



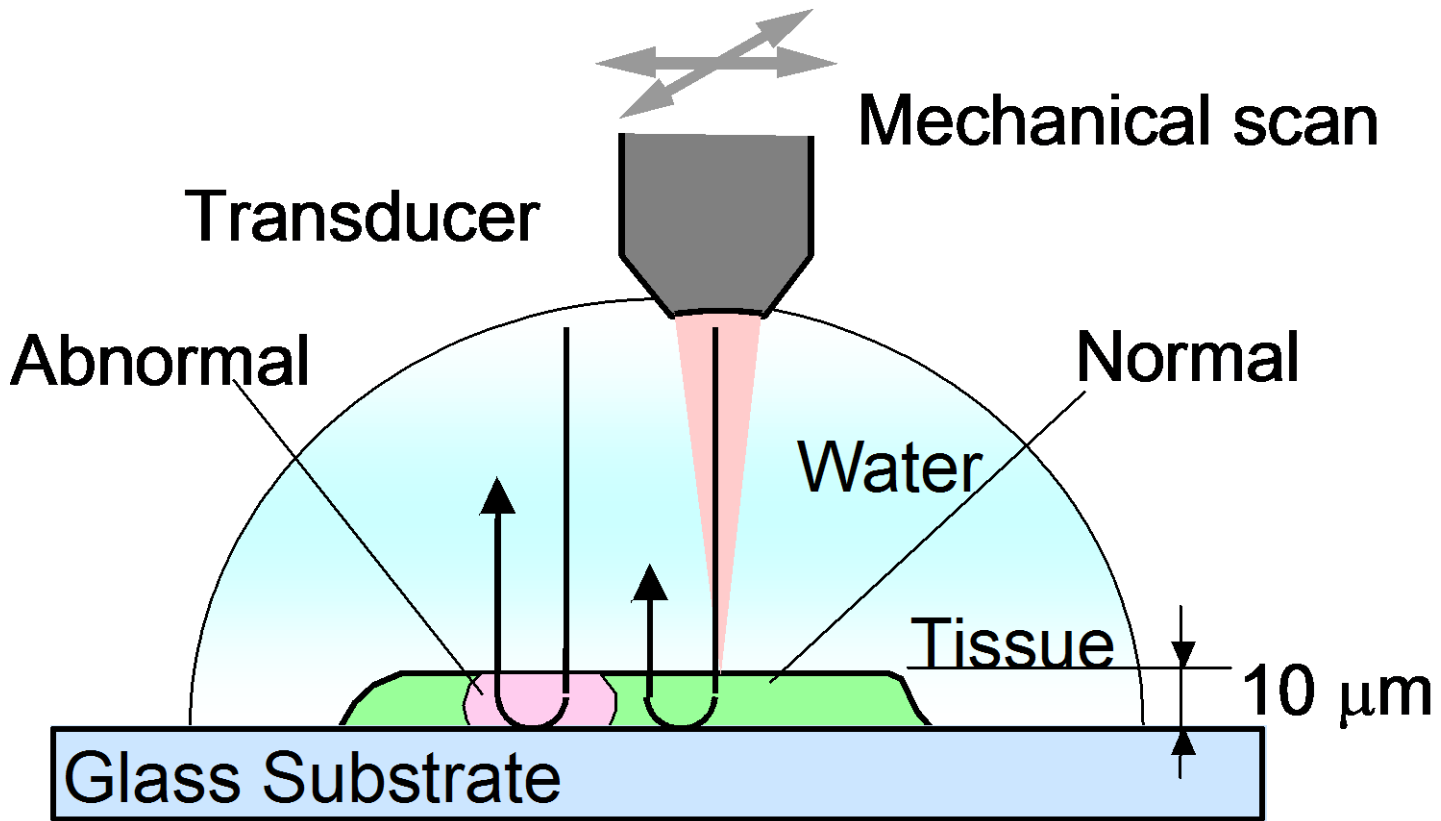
そのあと懇親会があった...

Sound Speed Microscope

Acoustic Impedance Microscope

Scanning Sound Speed Microscopy

Basic idea.



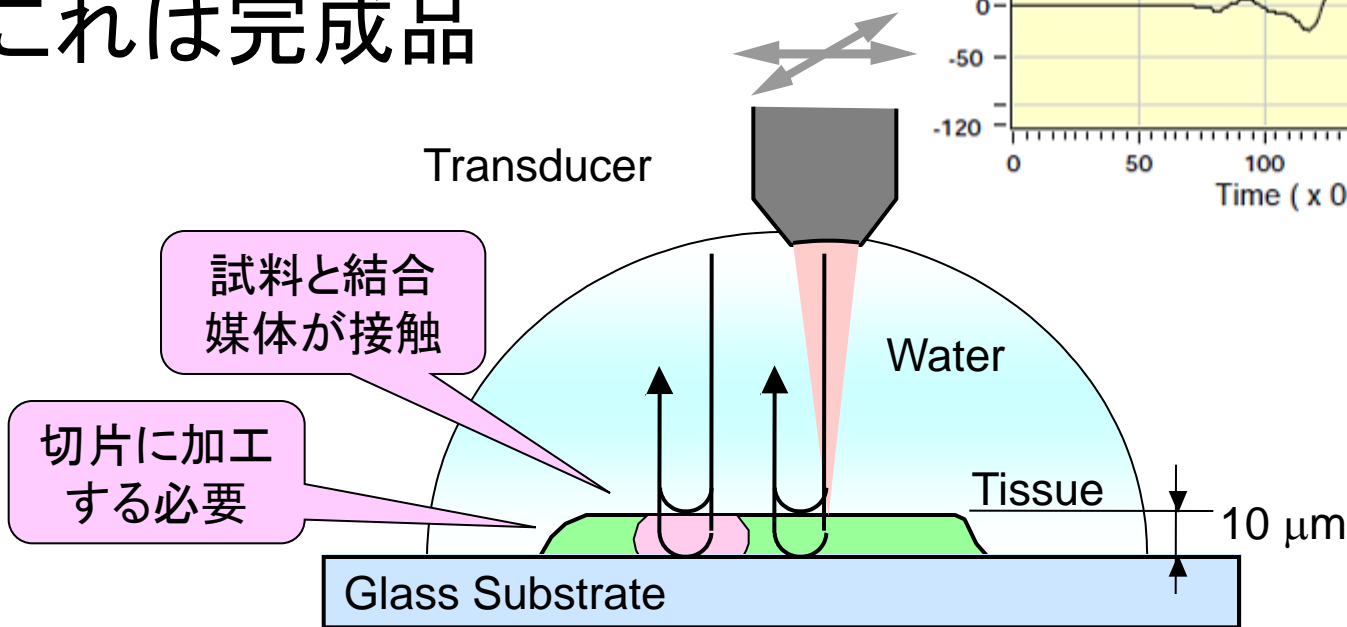
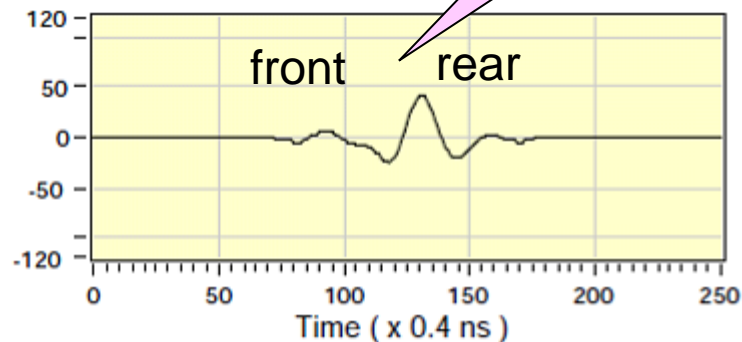
Visualize sound speed and attenuation.

生体組織の音速を測定する超音波顕微鏡

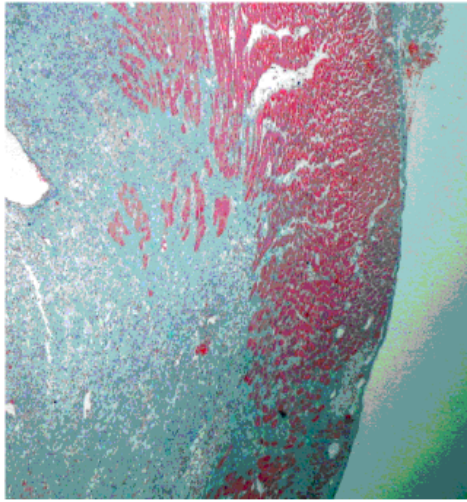


これは完成品

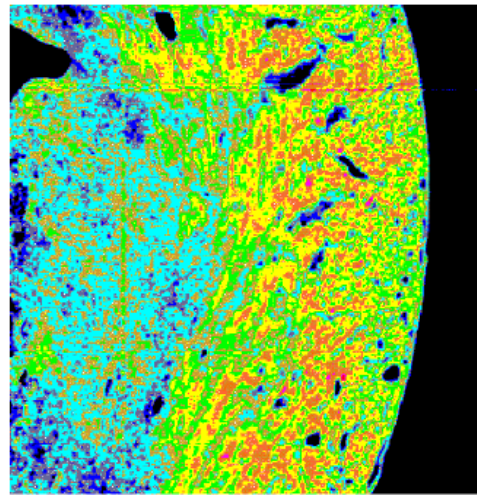
時間差測定
精度の影響



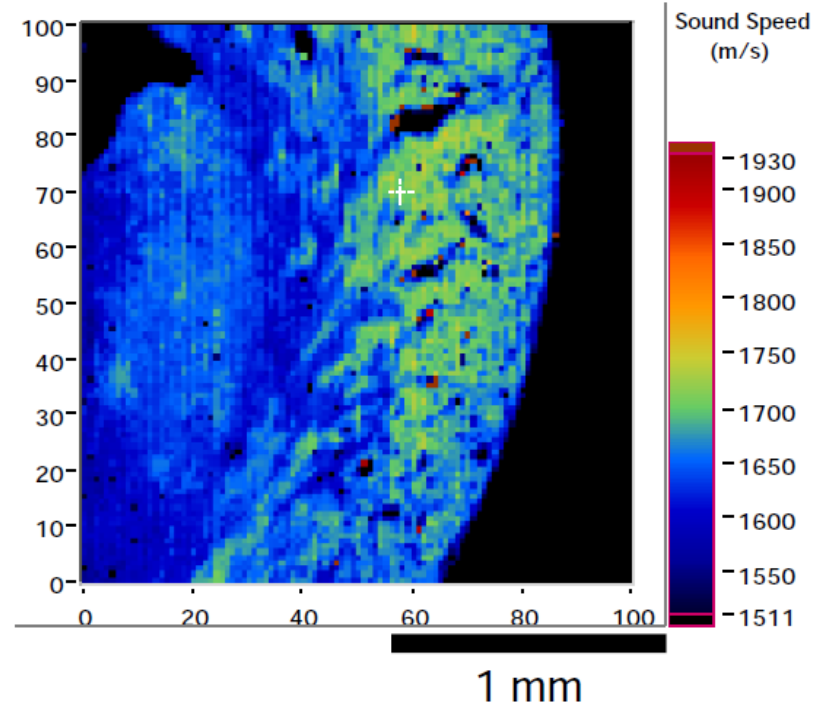
綺麗な絵が見えた。



Optical
microscopy
(stained)



Conventional frequency
domain measurement
(1 hr)

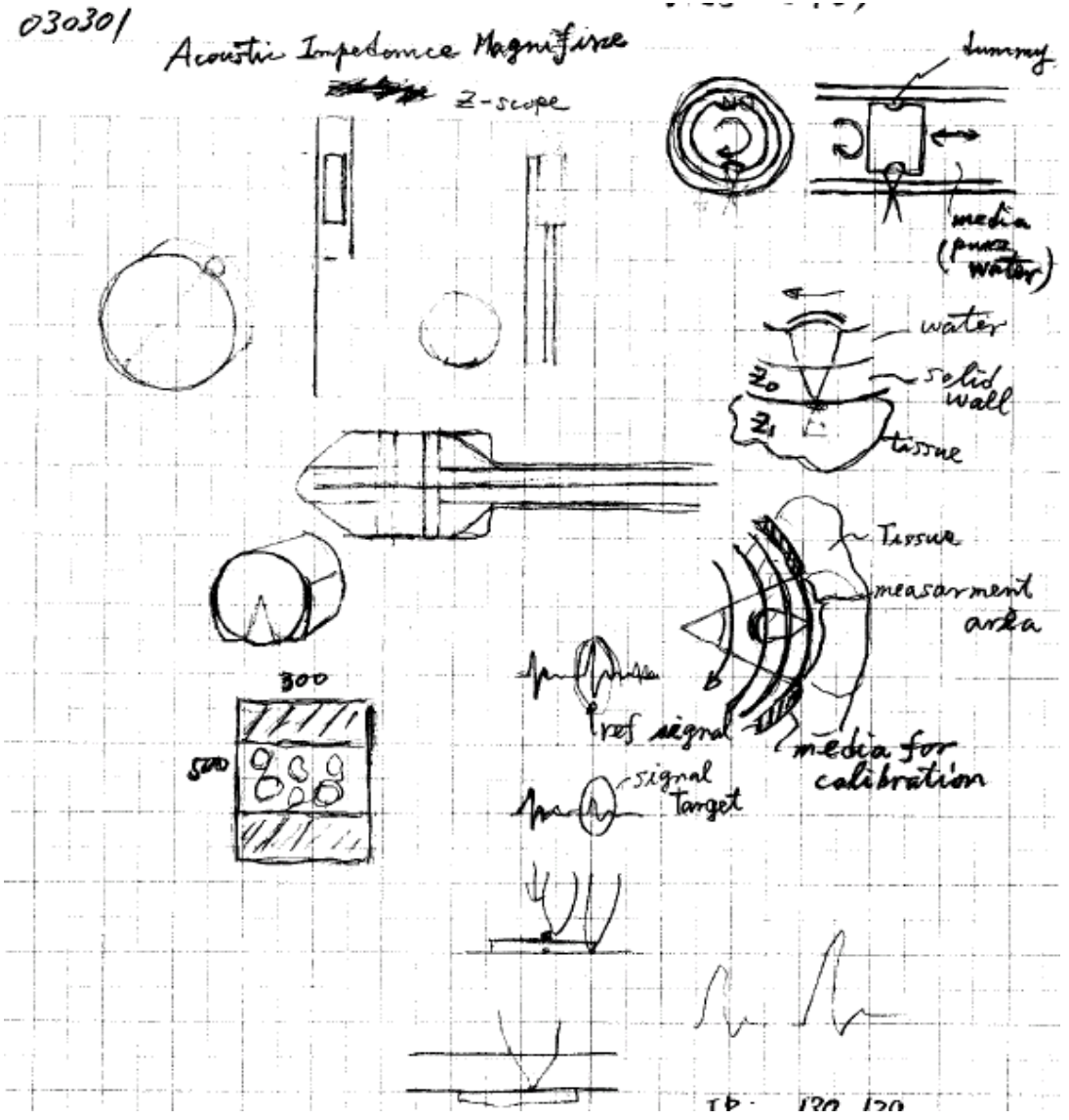


Pulse driven type
(10 min)

Massive hyalinization in the endocardial side (left side of the figure)
classified as severe allograft rejection.

Scanning Acoustic Impedance Microscopy

音響インピーダンス顕微鏡



(2003年3月1日)

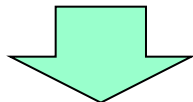
音響インピーダンス顕微鏡開発の目的。



試料を置くだけで観察できる

染色も切片作製も不要

This illustration shows a person looking through a microscope. A callout box points to the sample on the petri dish, stating that observation is possible simply by placing the sample. Below the microscope, a yellow box highlights a pink sample on a petri dish, with text indicating that staining and section preparation are unnecessary.



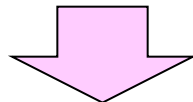
今進めている研究



プローブで観察できる

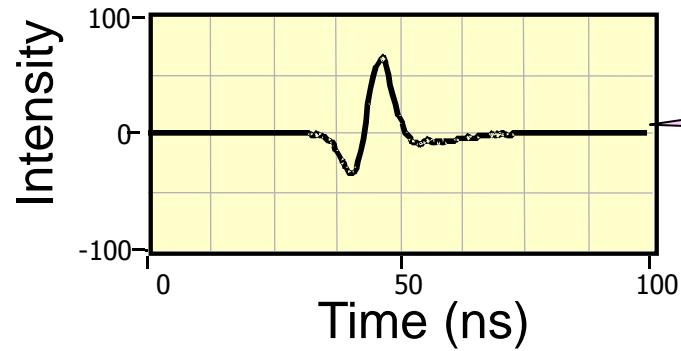
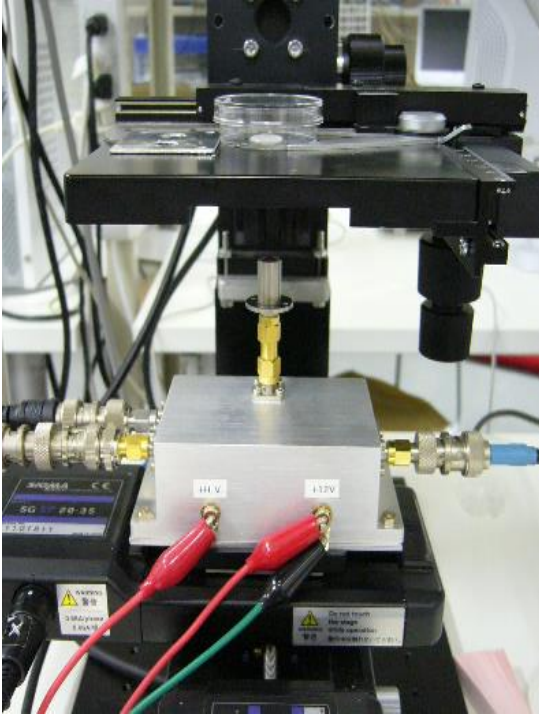
顕微プローブ

This illustration shows a surgeon in blue scrubs and a mask, using a probe on a patient. A monitor displays a microscopic view of the tissue. A callout box points to the probe, stating that observation is possible with the probe. Below the scene, the text '顕微プローブ' (Micro-probe) is written.



将来像？

概念図



信号強度のみを測定

切片加工不要

Reference

Target



試料と非接触

Transducer

Signal

Trigger

Pulsar-receiver

Internal bus

A/D board

GPIB

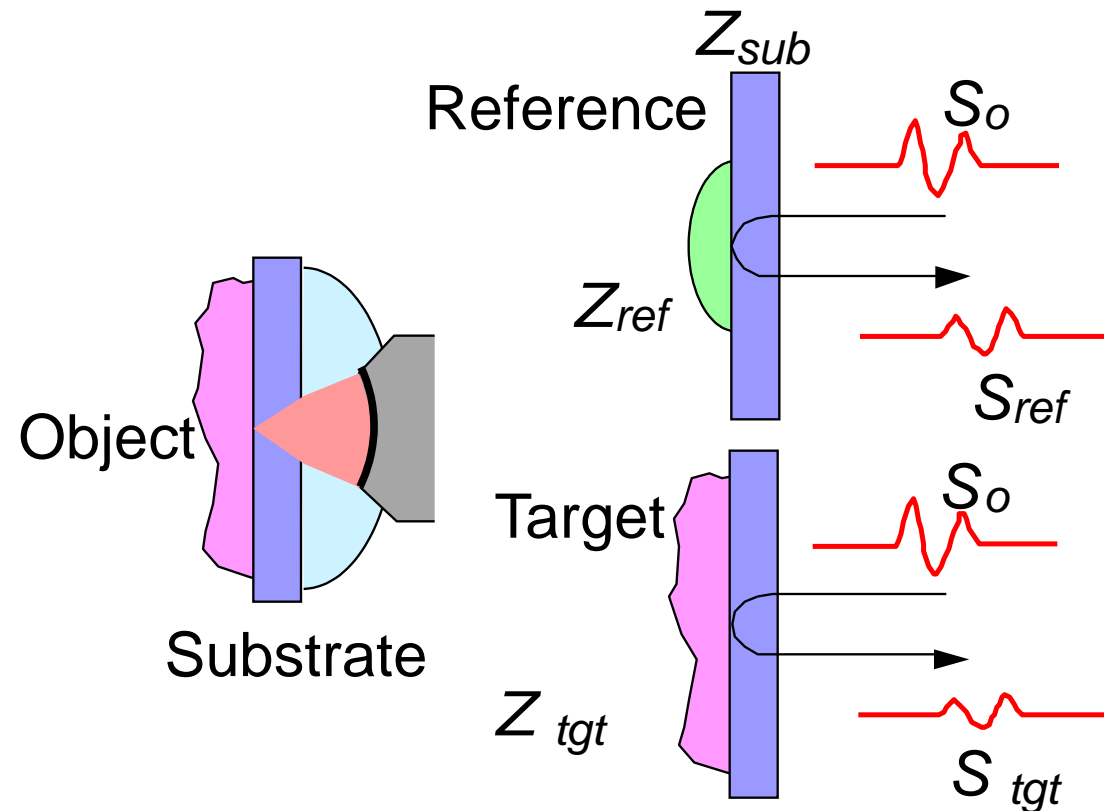
Stage Driver

Control

Mechanical stage



反射信号強度を音響インピーダンスに変換。



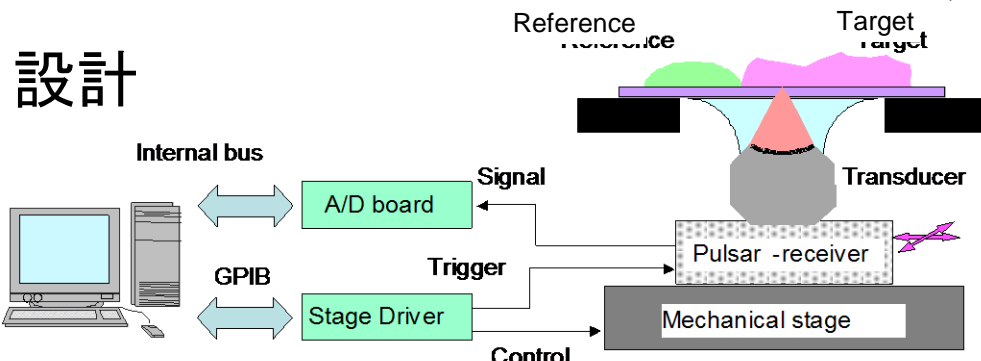
$$S_{ref} = \frac{Z_{ref} - Z_{sub}}{Z_{ref} + Z_{sub}} S_0$$

$$S_{tgt} = \frac{Z_{tgt} - Z_{sub}}{Z_{tgt} + Z_{sub}} S_0$$

$$Z_{tgt} = \frac{1 + \frac{S_{tgt}}{S_0}}{1 - \frac{S_{tgt}}{S_0}} Z_{sub} = \frac{1 - \frac{S_{tgt}}{S_{ref}} \cdot \frac{Z_{sub} - Z_{ref}}{Z_{sub} + Z_{ref}}}{1 + \frac{S_{tgt}}{S_{ref}} \cdot \frac{Z_{sub} - Z_{ref}}{Z_{sub} + Z_{ref}}} Z_{sub}$$

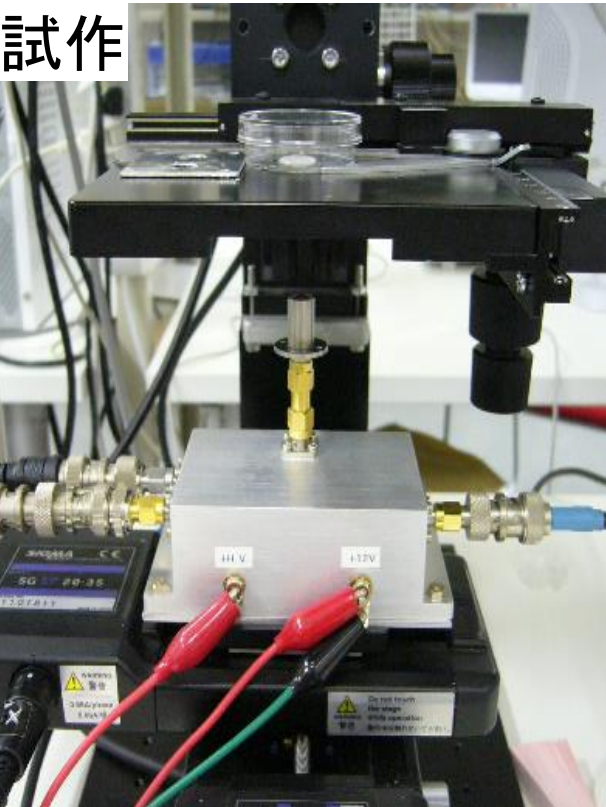
医学・生物学用超音波顕微鏡

設計

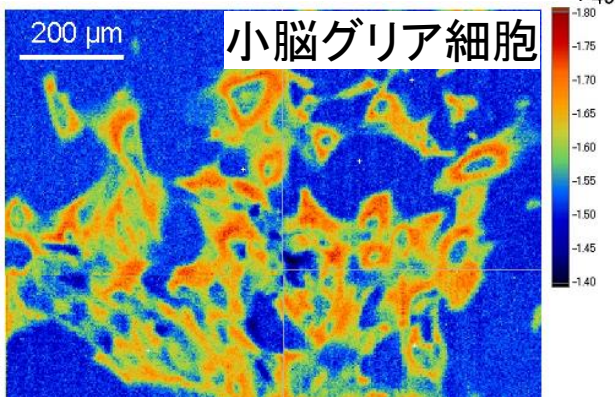
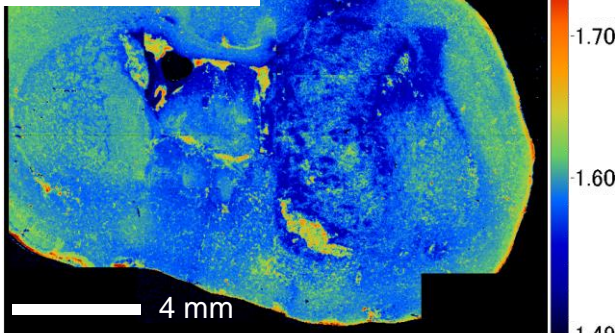


- (1) 高分子基板の上に試料を接触させる。
- (2) 集束超音波を走査。
- (3) 参照材料(水)を使って、反射強度を硬さに関係する情報(音響インピーダンス)に変換し画像化。

試作



観察解析 脳腫瘍組織



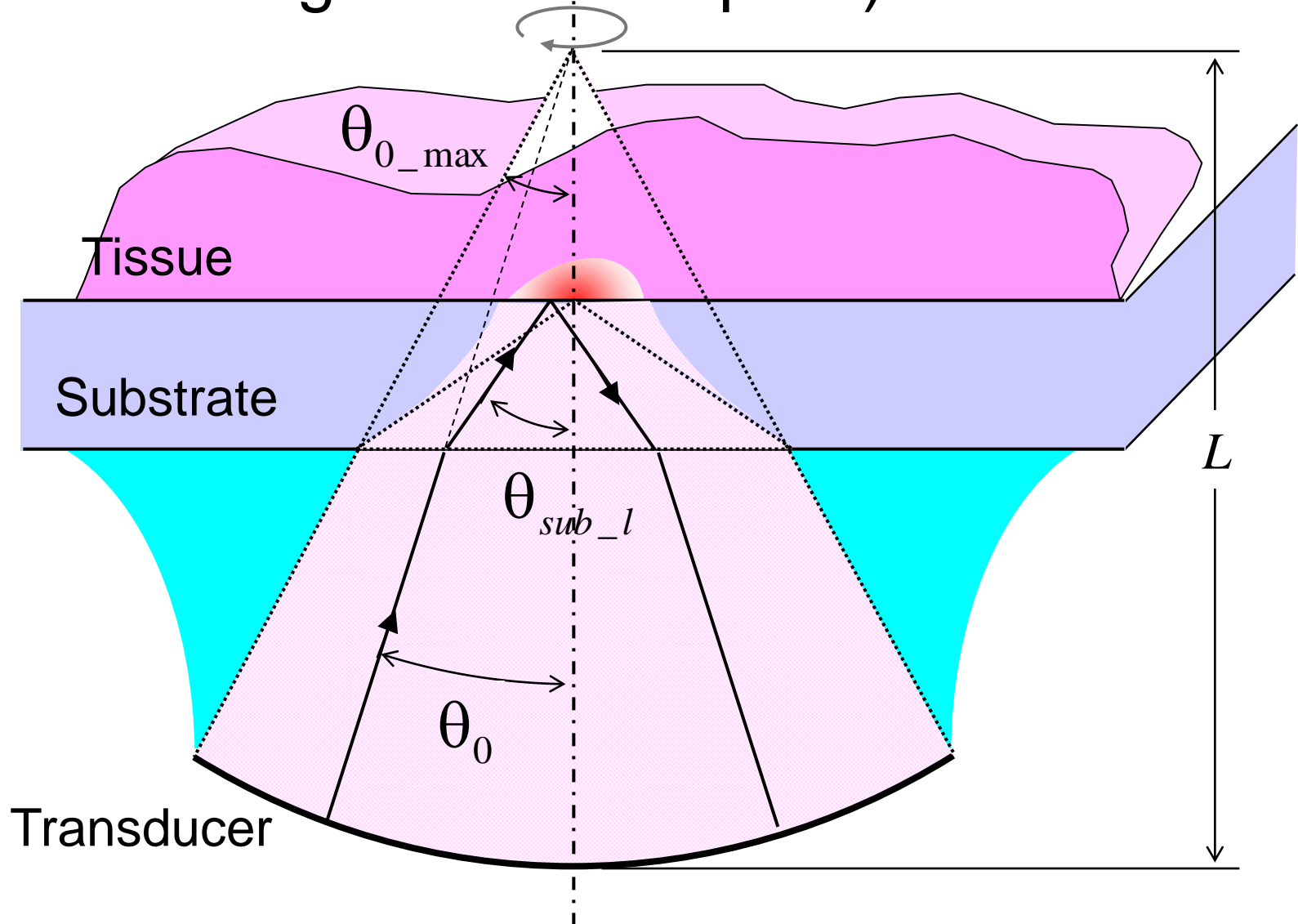
実用機

本多電子
AMS-50SI

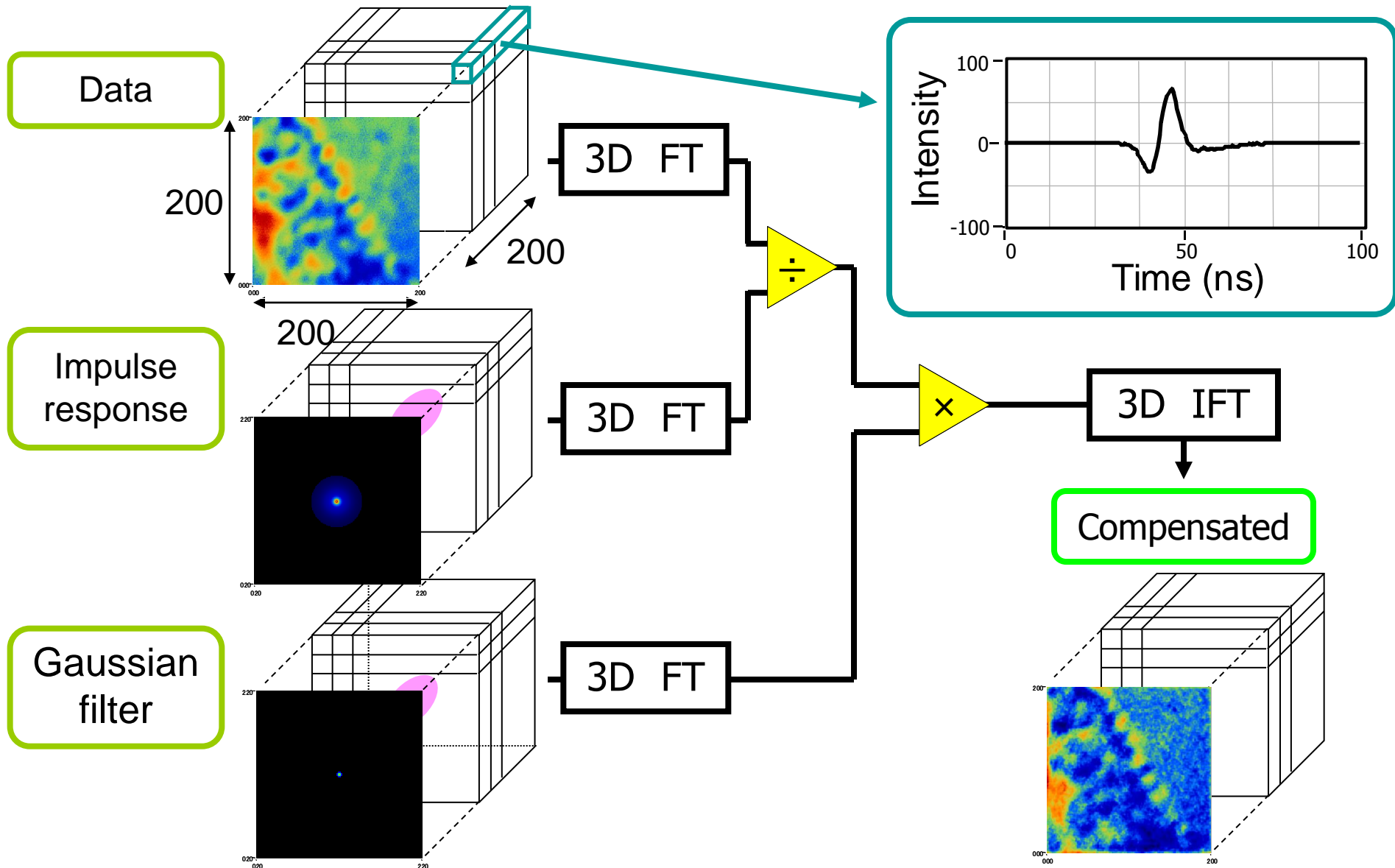
浜松医科大・東北大学・
本多電子(株)との共同研究I

Improvement of spatial resolution

Aberration produced by the substrate (on the basis of geometrical-optics)

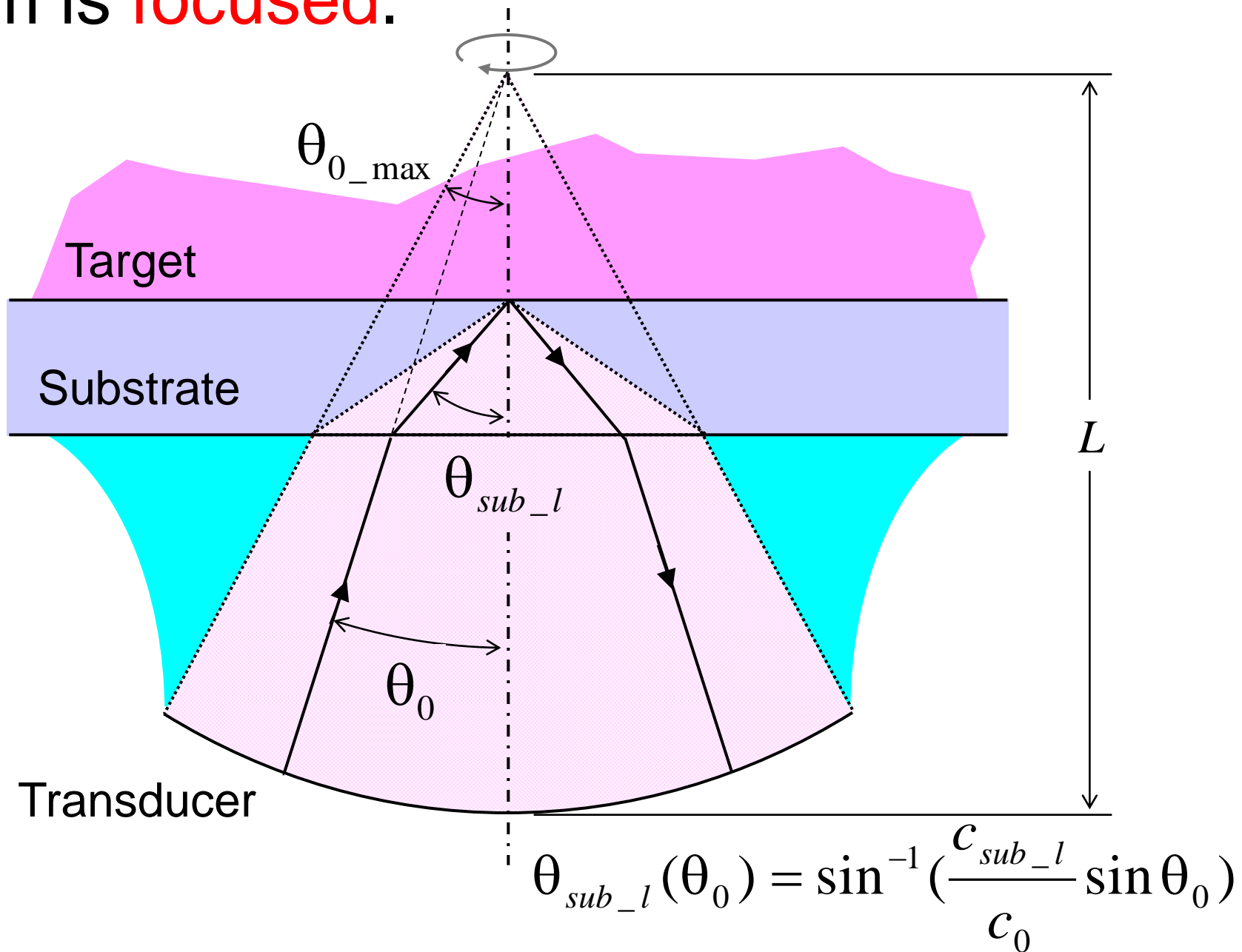


3D deconvolution processing

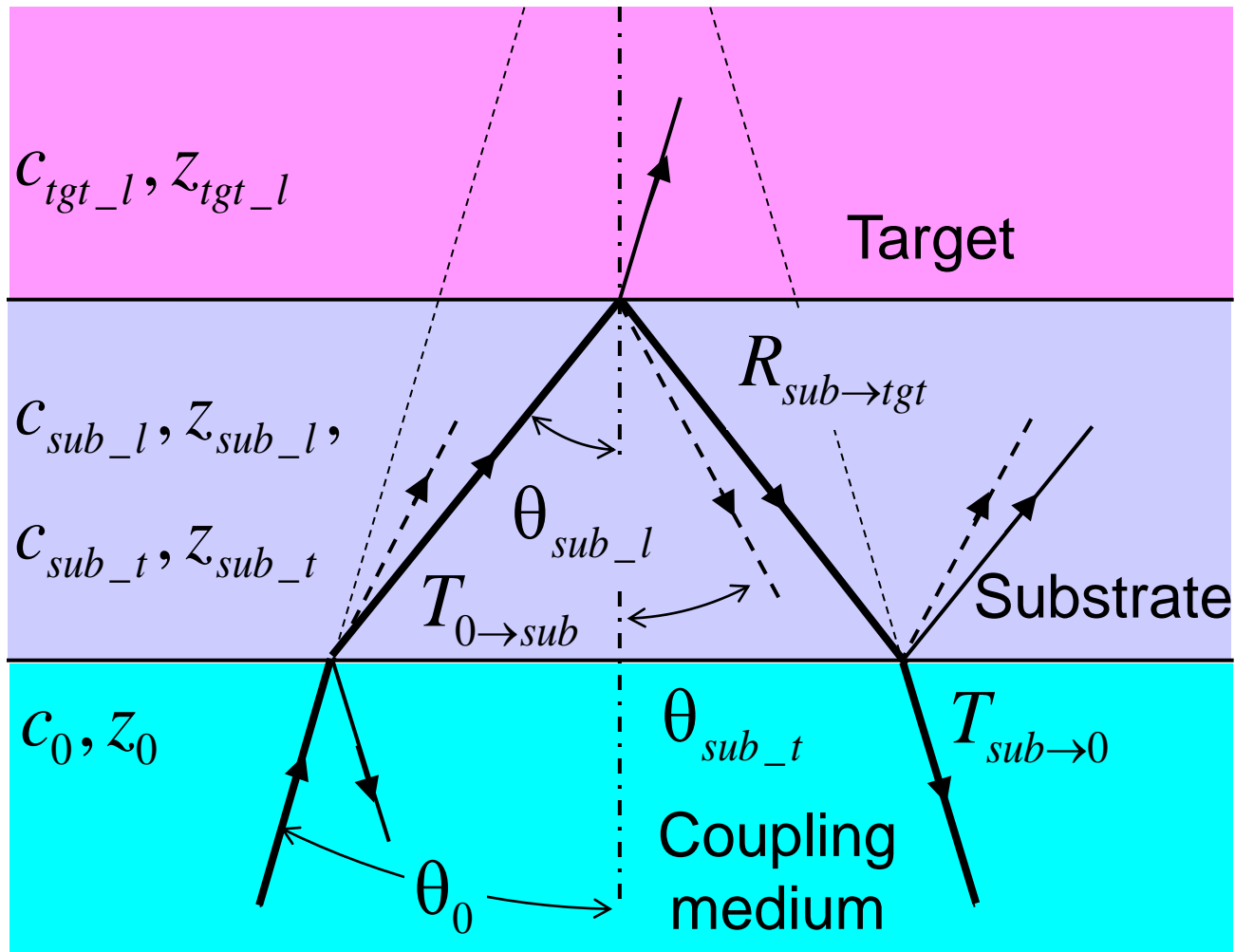


Improvement of accuracy

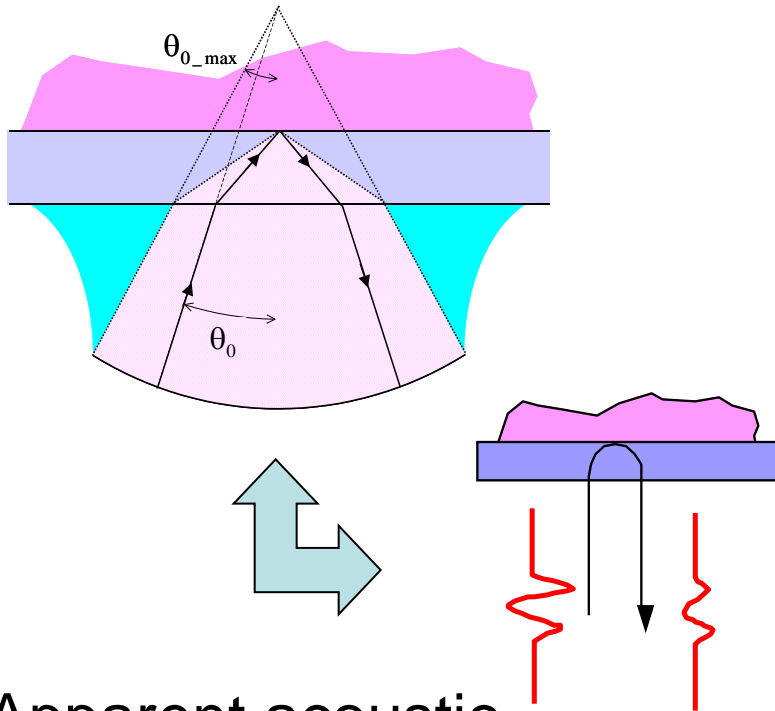
Beam is **focused**.



Wave propagation.



Apparent acoustic impedance of the target assuming vertical incidence.



Apparent reflection constant target:

$$S_{tgt}(\underline{Z}_{tgt}, c_{tgt}, \theta_{0_max}) / S_0 = \int_0^{\theta_{0_max}} 2\pi L^2 \sin \theta_0 R_{sub \rightarrow tgt}(\theta_0) T'_{0 \rightarrow sub}(\theta_0) d\theta_0$$

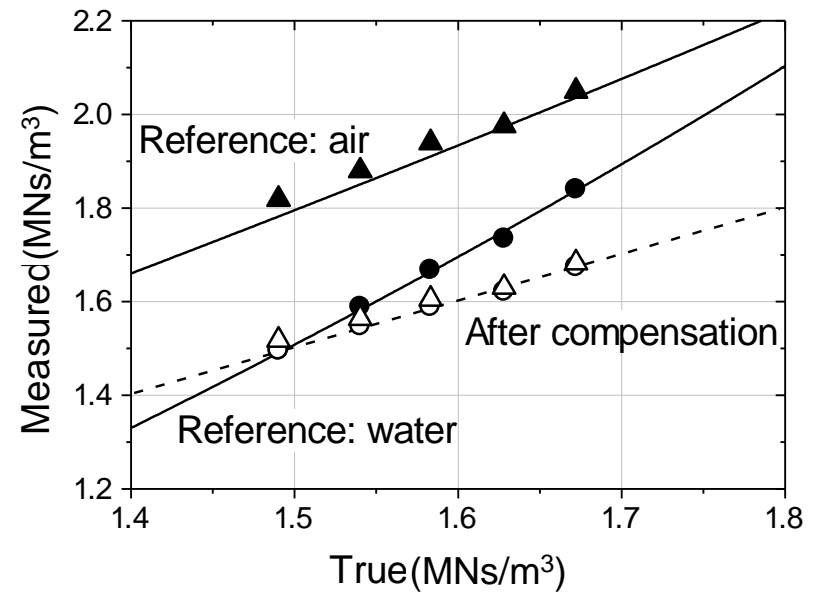
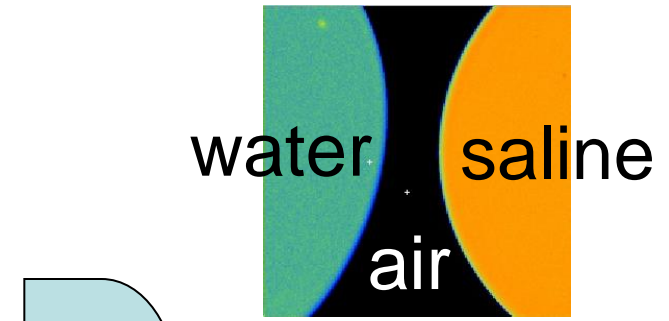
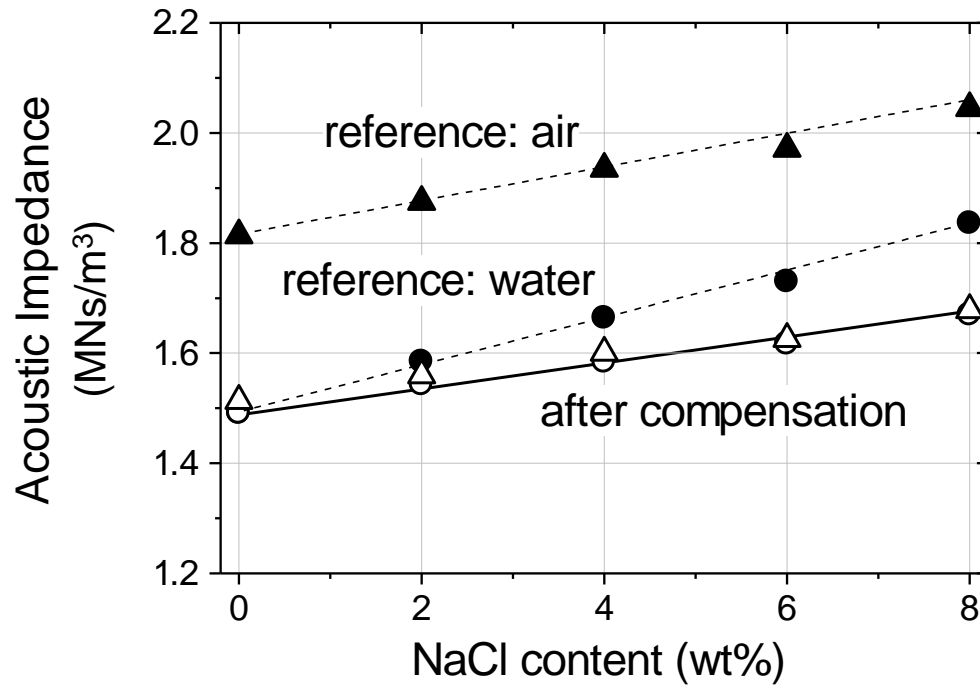
reference:

$$S_{ref}(Z_{ref}, c_{ref}, \theta_{0_max}) / S_0 = \int_0^{\theta_{0_max}} 2\pi L^2 \sin \theta_0 R_{sub \rightarrow ref}(\theta_0) T'_{0 \rightarrow sub}(\theta_0) d\theta_0$$

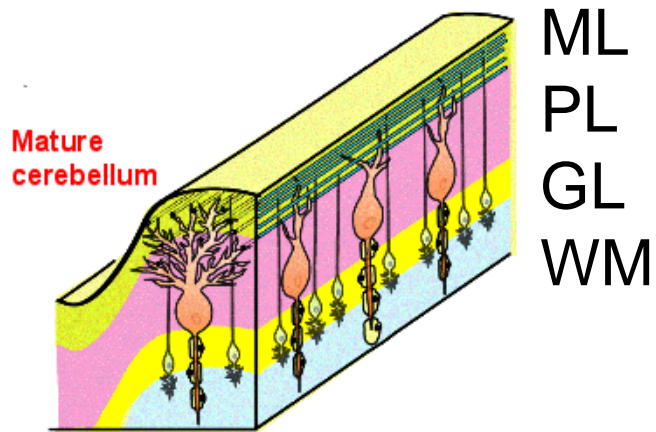
Apparent acoustic impedance of the target:

$$\underline{Z}_{tgt_app} = \frac{1 + \frac{S_{tgt}(\underline{Z}_{tgt}, c_{tgt}, \theta_{0_max})}{S_{ref}(Z_{ref}, c_{ref}, \theta_{0_max})} \cdot \frac{Z_{ref} - Z_{sub_l}}{Z_{ref} + Z_{sub_l}}}{1 - \frac{S_{tgt}(\underline{Z}_{tgt}, c_{tgt}, \theta_{0_max})}{S_{ref}(Z_{ref}, c_{ref}, \theta_{0_max})} \cdot \frac{Z_{ref} - Z_{sub_l}}{Z_{ref} + Z_{sub_l}}} \cdot Z_{sub_l}$$

Measurement for saline solution.

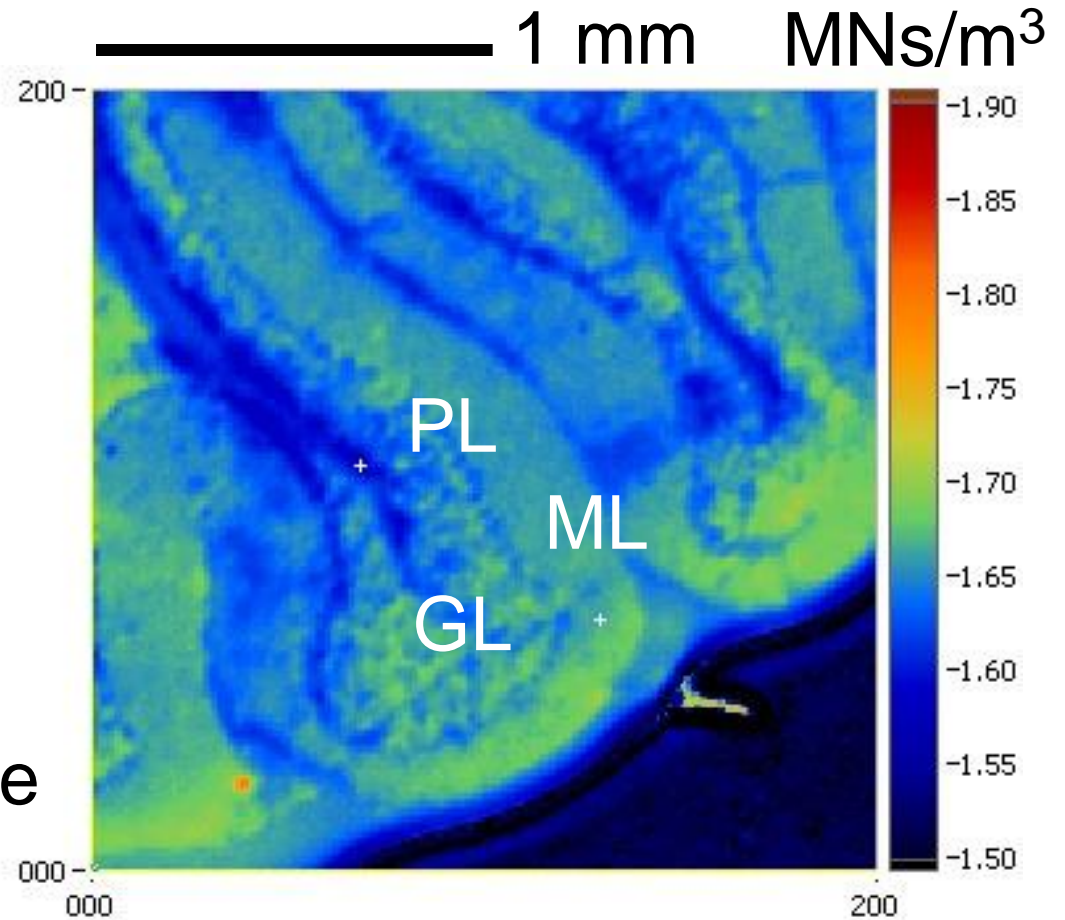


Cerebellum tissue of a rat.

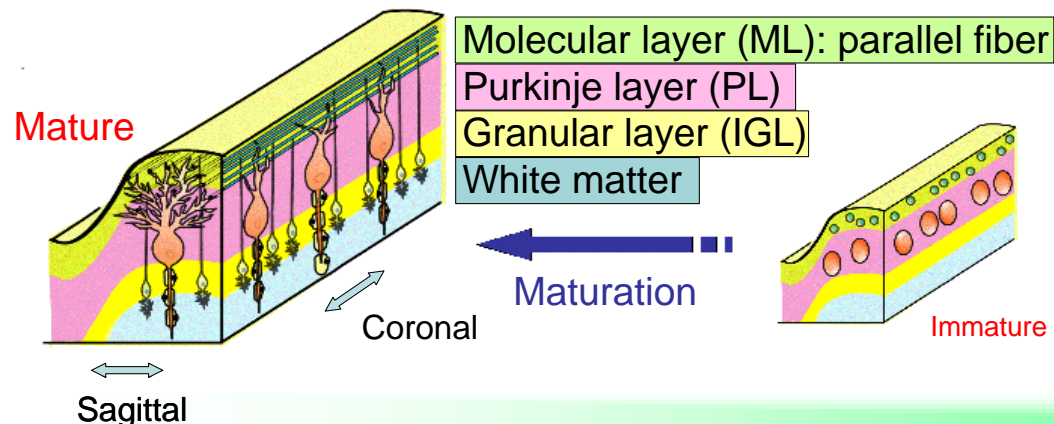
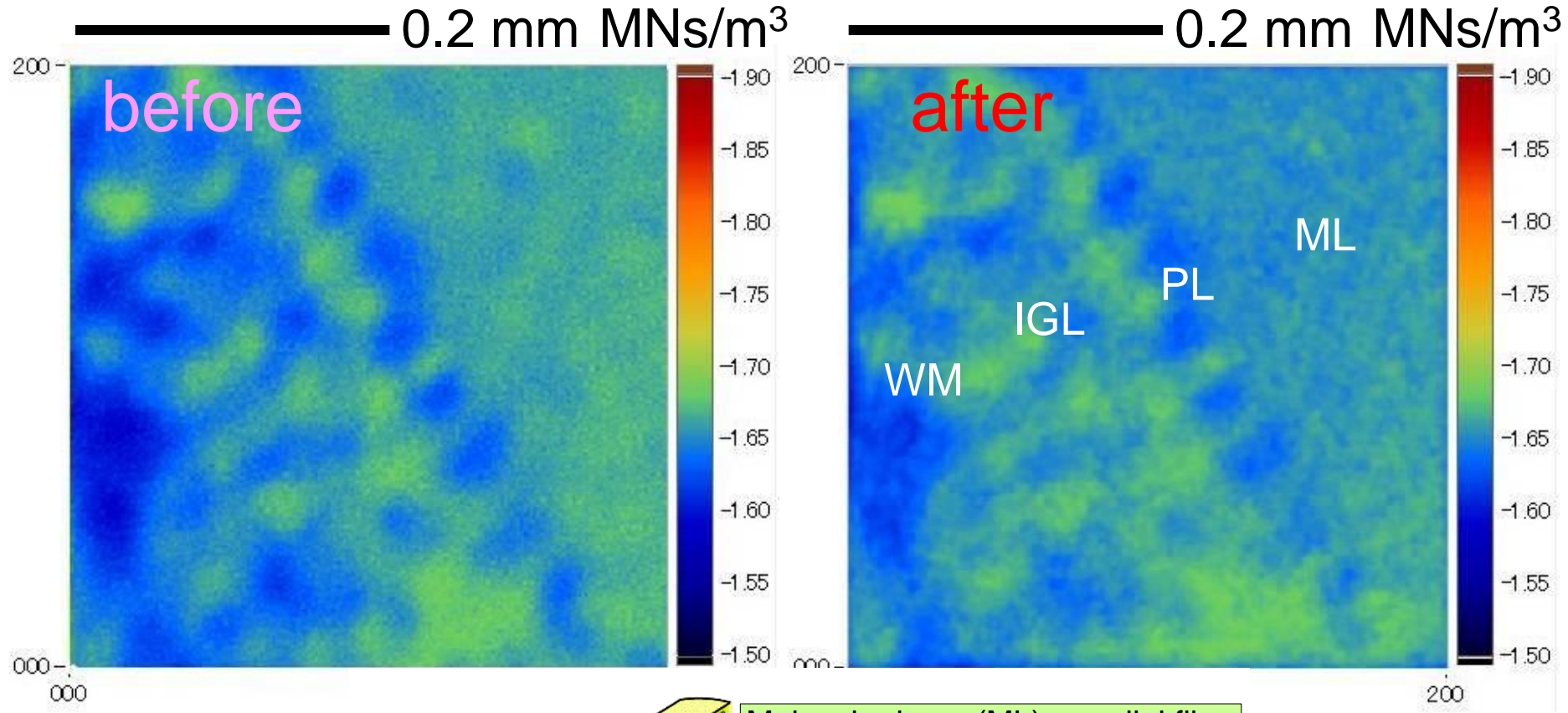


P15

fixation by formaldehyde

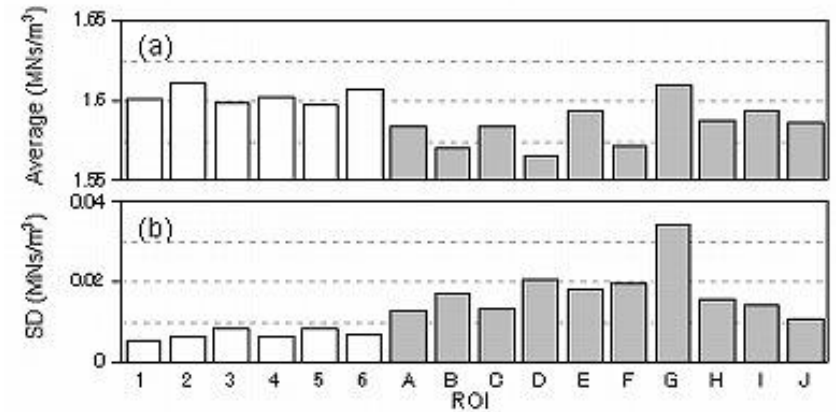
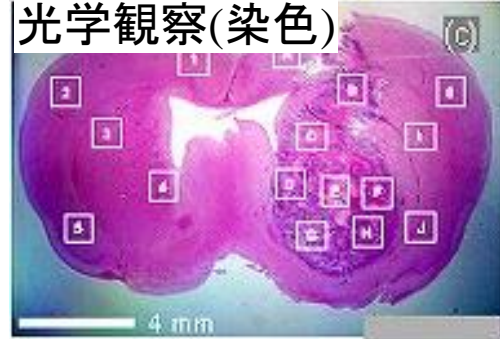
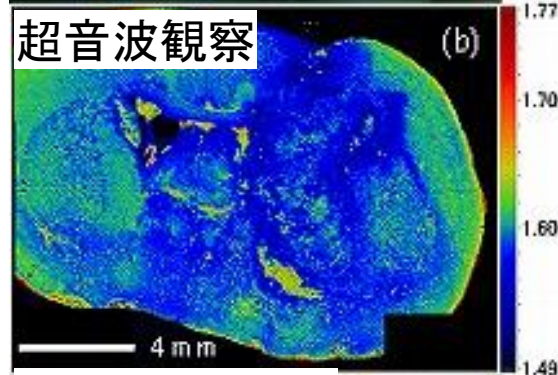
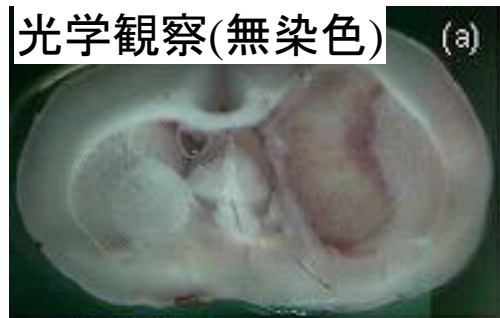


Acoustic impedance images

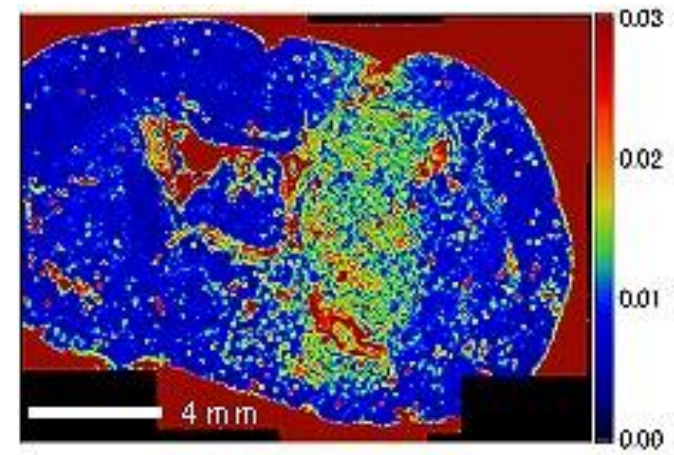


Observation of brain tumor model of rat

超音波顕微鏡による脳腫瘍組織観察



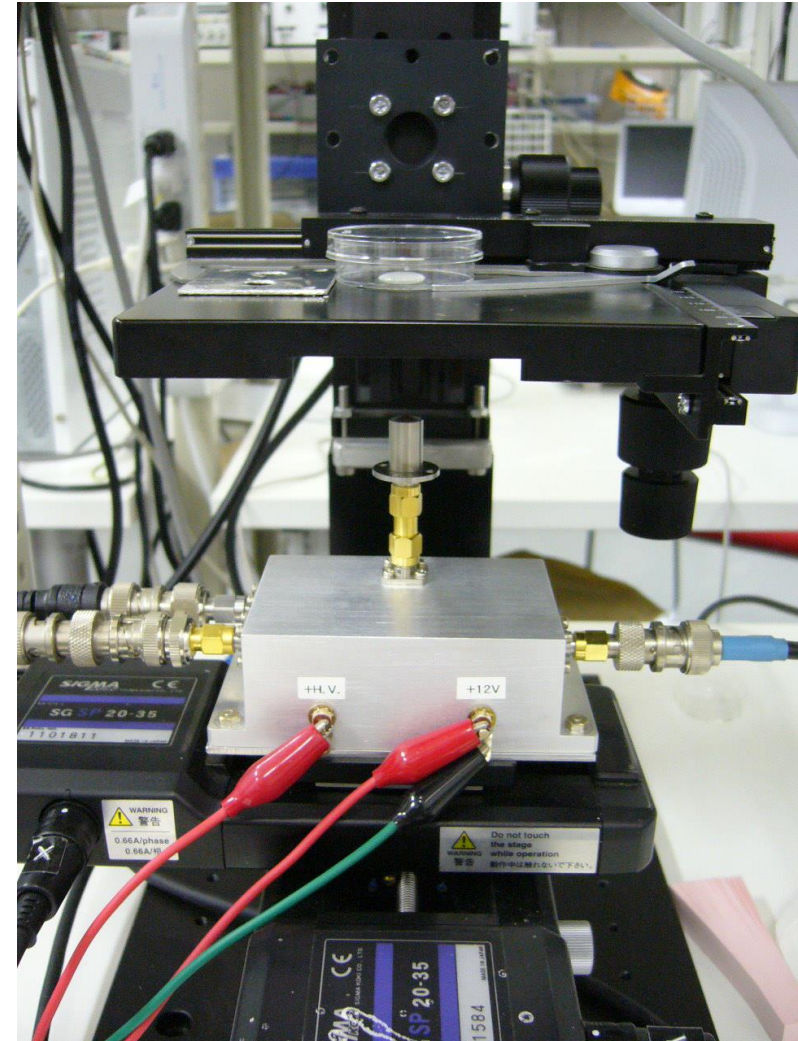
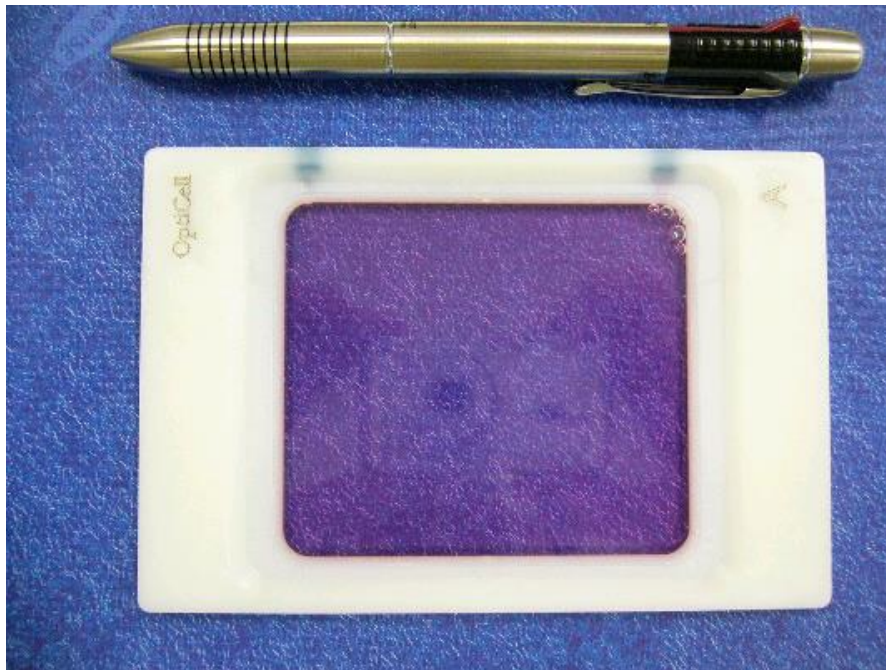
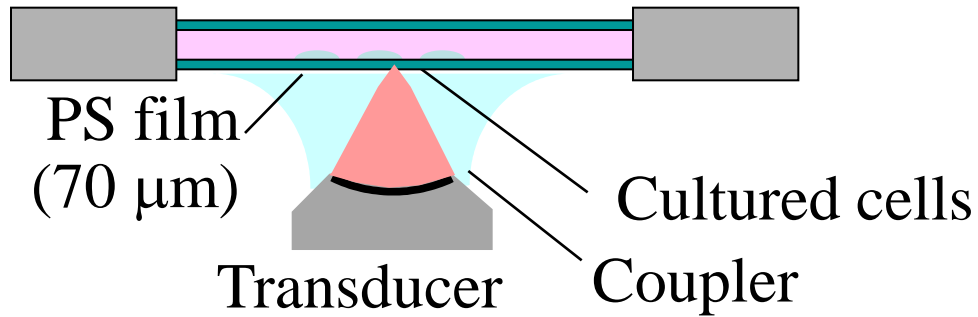
(a)音響インピーダンスの平均値
 (b)音響インピーダンスのばらつき(標準偏差)
 白いバーは健全部、黒いバーは患部。



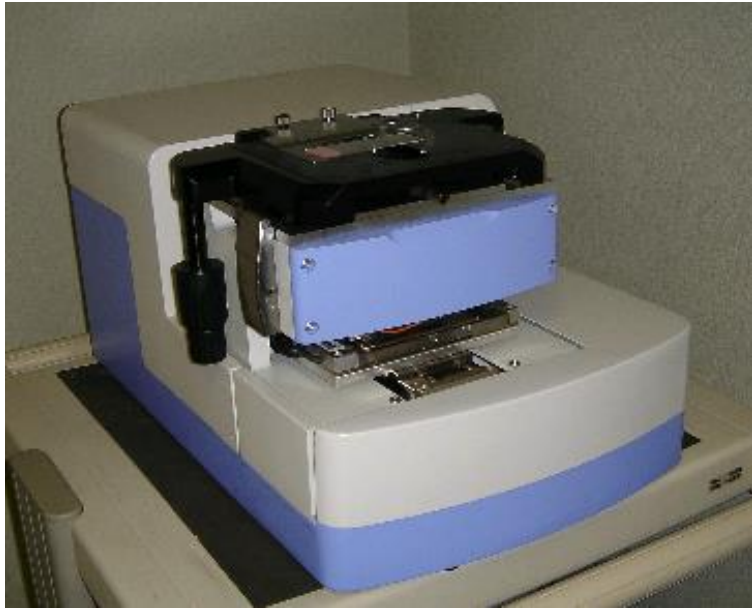
局所的な音響インピーダンスの粗さを画像化し、患部をハイライト。

Cell size observation

Observation system for cultured cells.



Commercialized system by Honda Electronics.



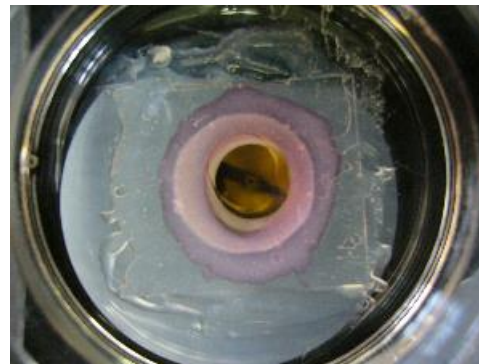
body (new type available)



stage



dish

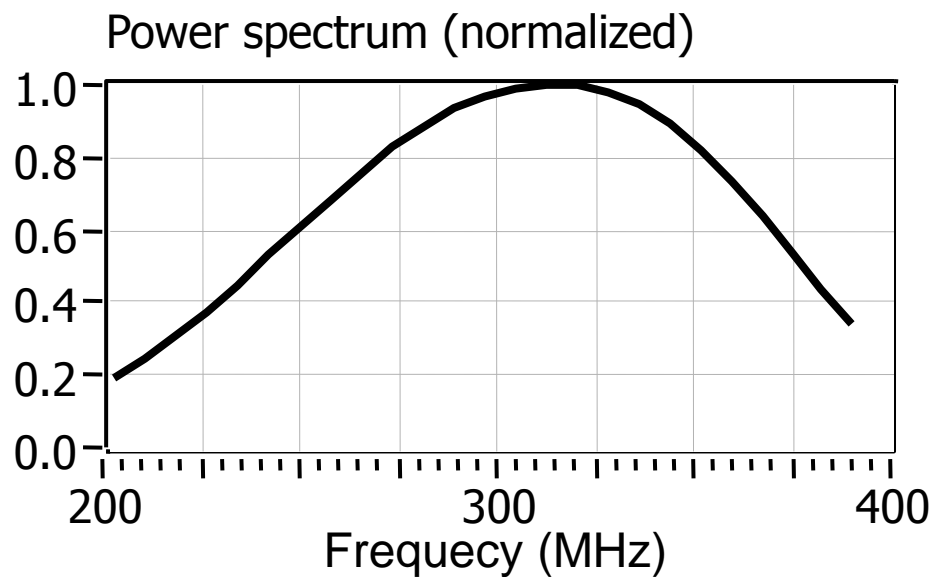
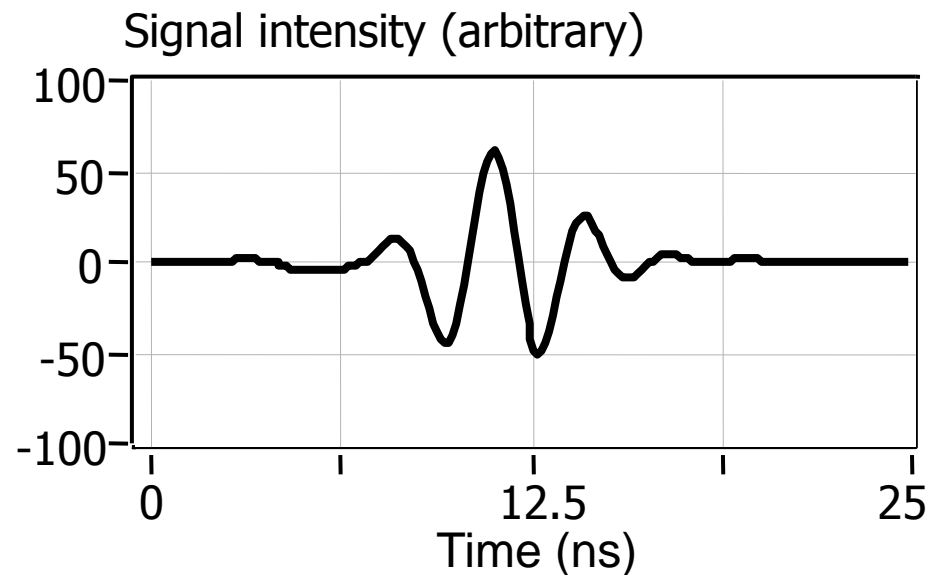


dish with film



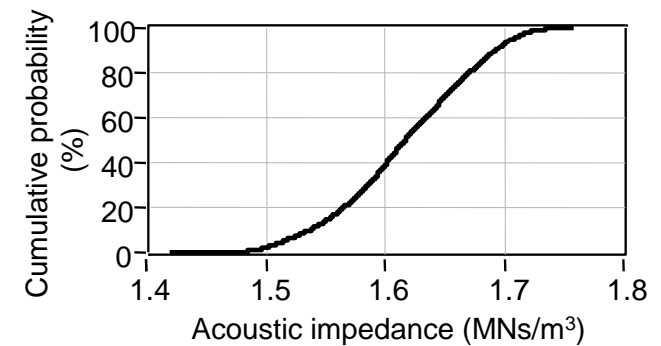
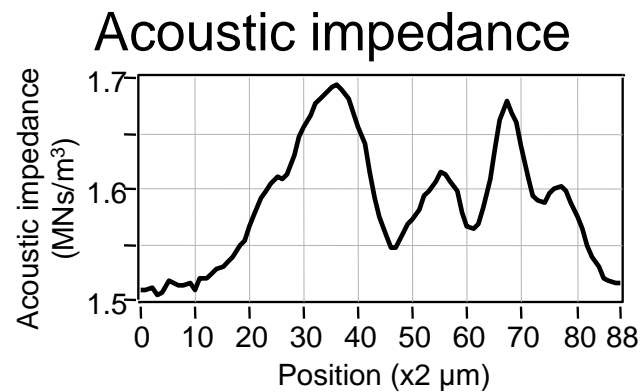
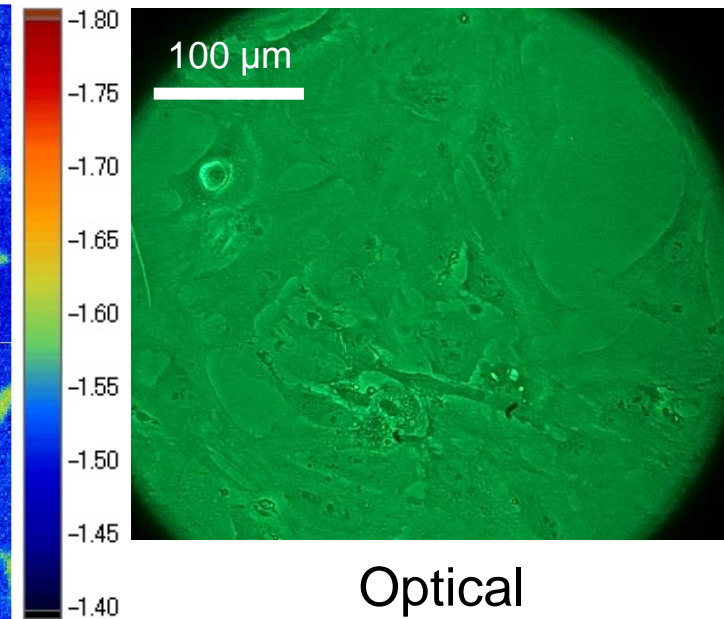
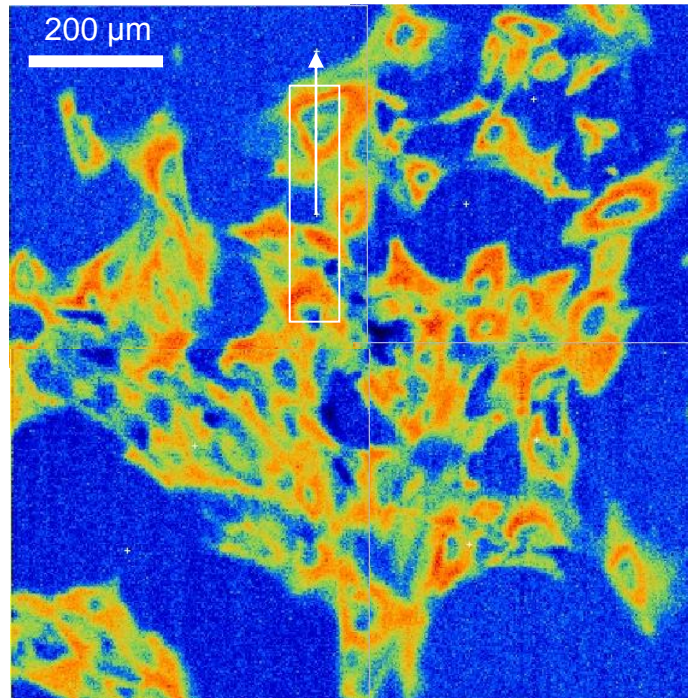
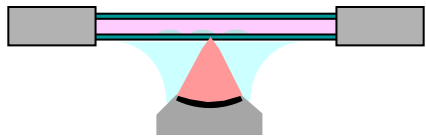
incubation cell

Waveform and spectrum.



200~400 MHz
range was used.

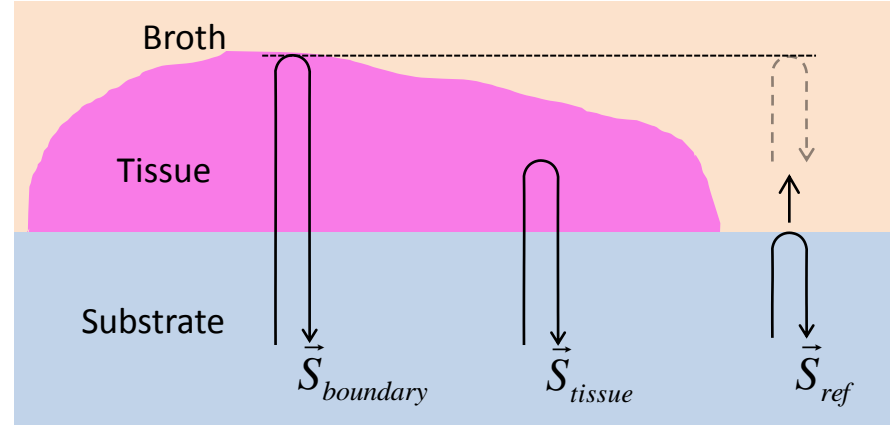
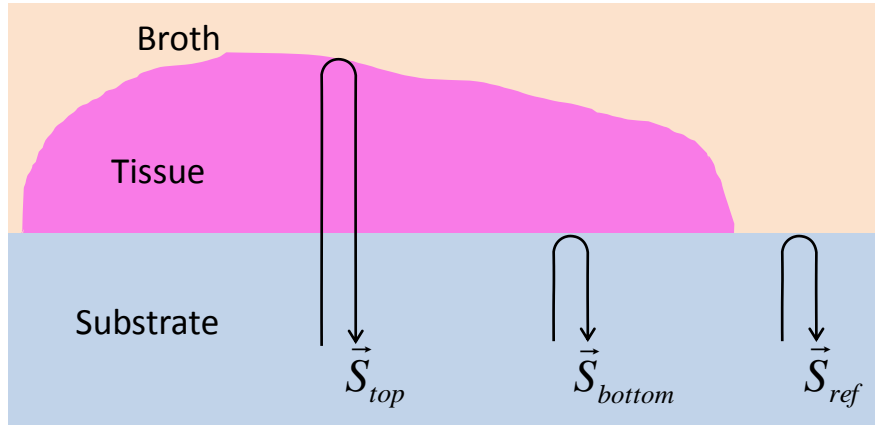
Cultured glial cells, rat.



Trace along the white arrow

Distribution in the ROI

信号の分離方法



$$\vec{S}_{tgt} = \vec{S}_{bottom} + \vec{S}_{top} = \frac{|\vec{S}_{tgt}| \cdot \cos\theta}{|\vec{S}_{ref}|} \cdot \vec{S}_{ref} + \vec{S}_{top}$$

$$\vec{S}_{top} = \vec{S}_{tgt} - \frac{|\vec{S}_{tgt}| \cdot \cos\theta}{|\vec{S}_{ref}|} \cdot \vec{S}_{ref}$$

$$\vec{S}_{top} = \vec{S}_{boundary} + \vec{S}_{tissue} = \frac{|\vec{S}_{top}| \cdot \cos\theta'}{|\vec{S}_{ref}|} \cdot \vec{S}_{ref} + \vec{S}_{tissue}$$

$$\vec{S}_{boundary} = \frac{|\vec{S}_{top}| \cdot \cos\theta'}{|\vec{S}_{ref}|} \cdot \vec{S}_{ref} \quad \vec{S}_{tissue} = \vec{S}_{top} - \vec{S}_{boundary}$$

\vec{S}_{ref} : 参照信号 \vec{S}_{tgt} : 標的的信号 \vec{S}_{bottom} : 基板と細胞との界面からの反射信号

\vec{S}_{top} : 細胞内部および上面からの反射信号 \vec{S}_{tissue} : 細胞内部からの反射信号 $\vec{S}_{boundary}$: 細胞上面からの反射信号

厚さと音響インピーダンス

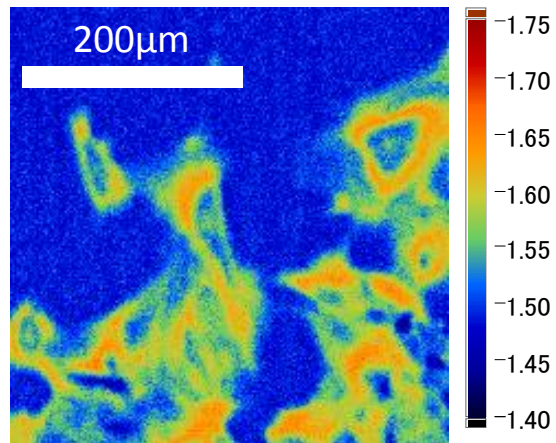


Fig.1 Acoustic impedance image of astrocyte cells indicated in MN/m^3 .

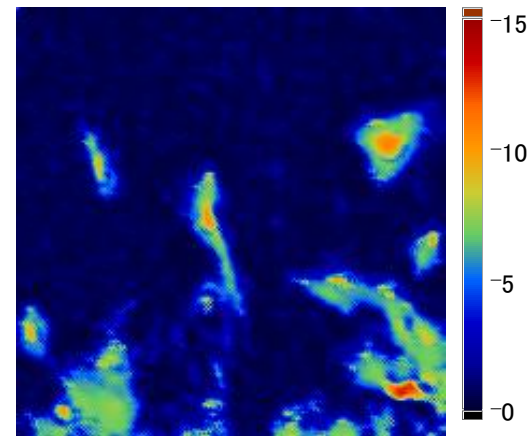
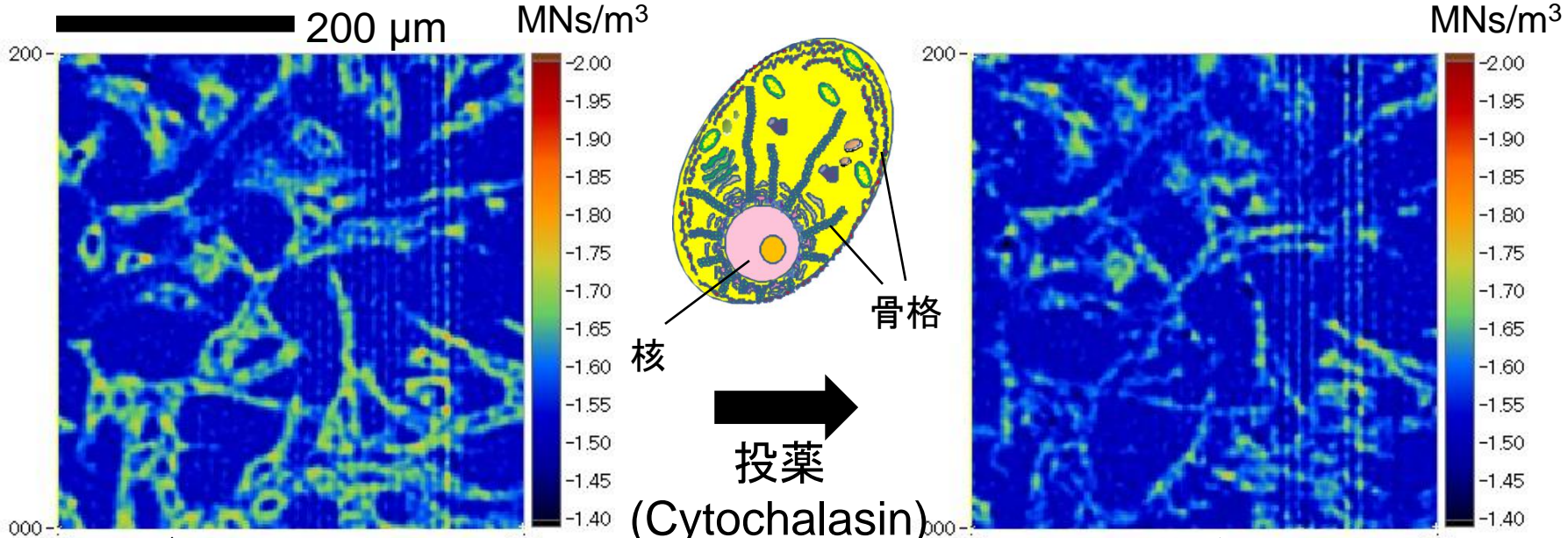


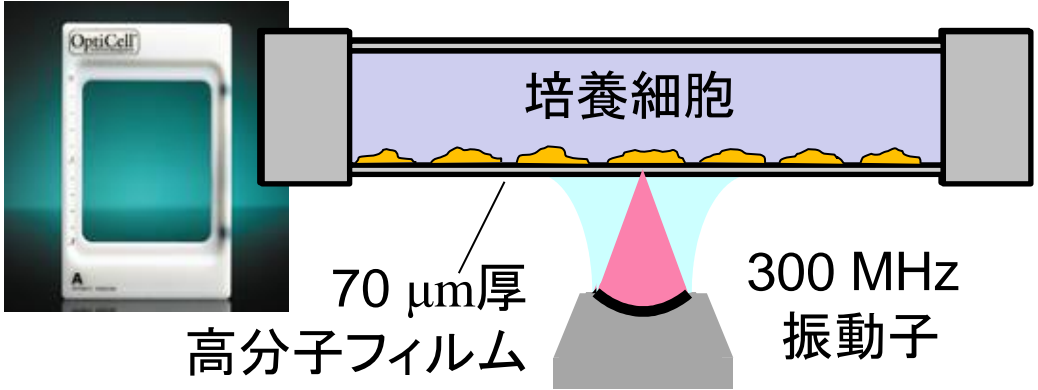
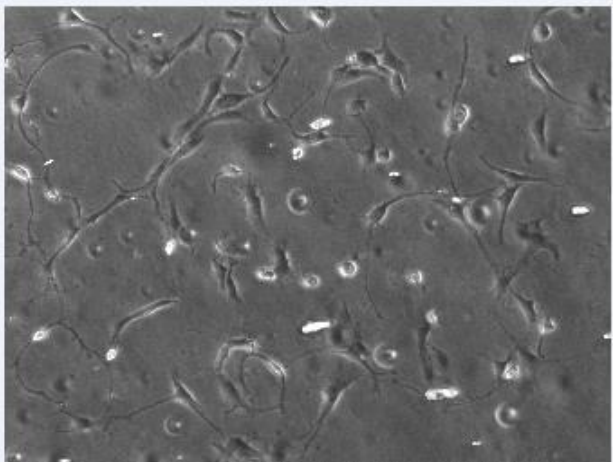
Fig.2 Thickness profile in μm . The height of each cell is about 12-13 μm .

細胞に対する投薬効果を生きたまま観察



ガン細胞(glioma)
明るい環の部分が細胞骨格

投薬後1時間
細胞骨格が崩れている

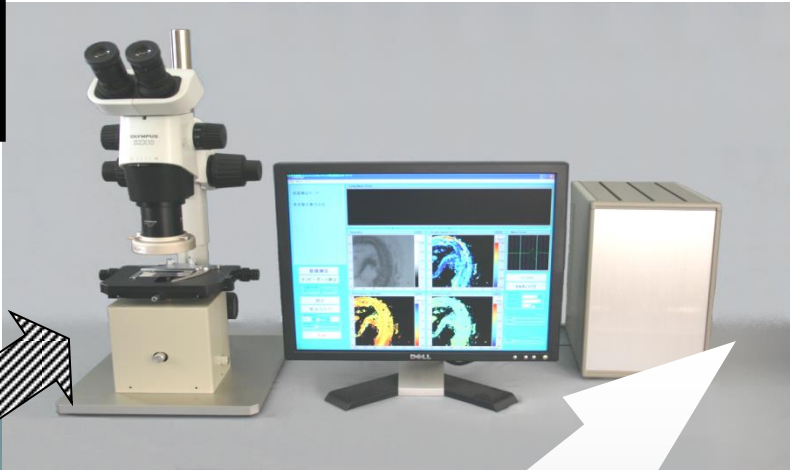


光学顕微鏡では内部構造が見えない

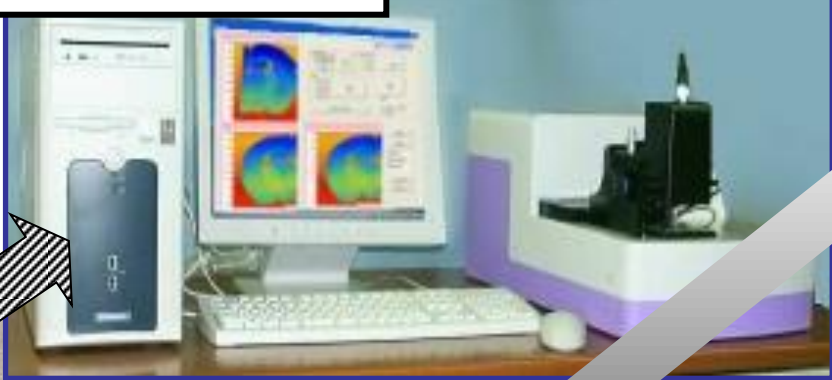
Commercialized by
HONDA Electronics

Development in Honda Electronics

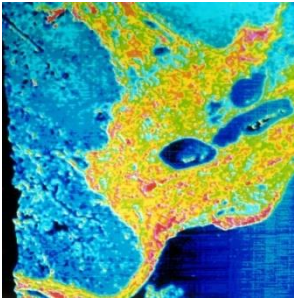
**2005 Pulse Driven Type
Ultrasonic Sound Speed Microscope**



**2007 Pulse Driven Type Ultrasonic
Sound Speed / Acoustic Impedance
Microscope**

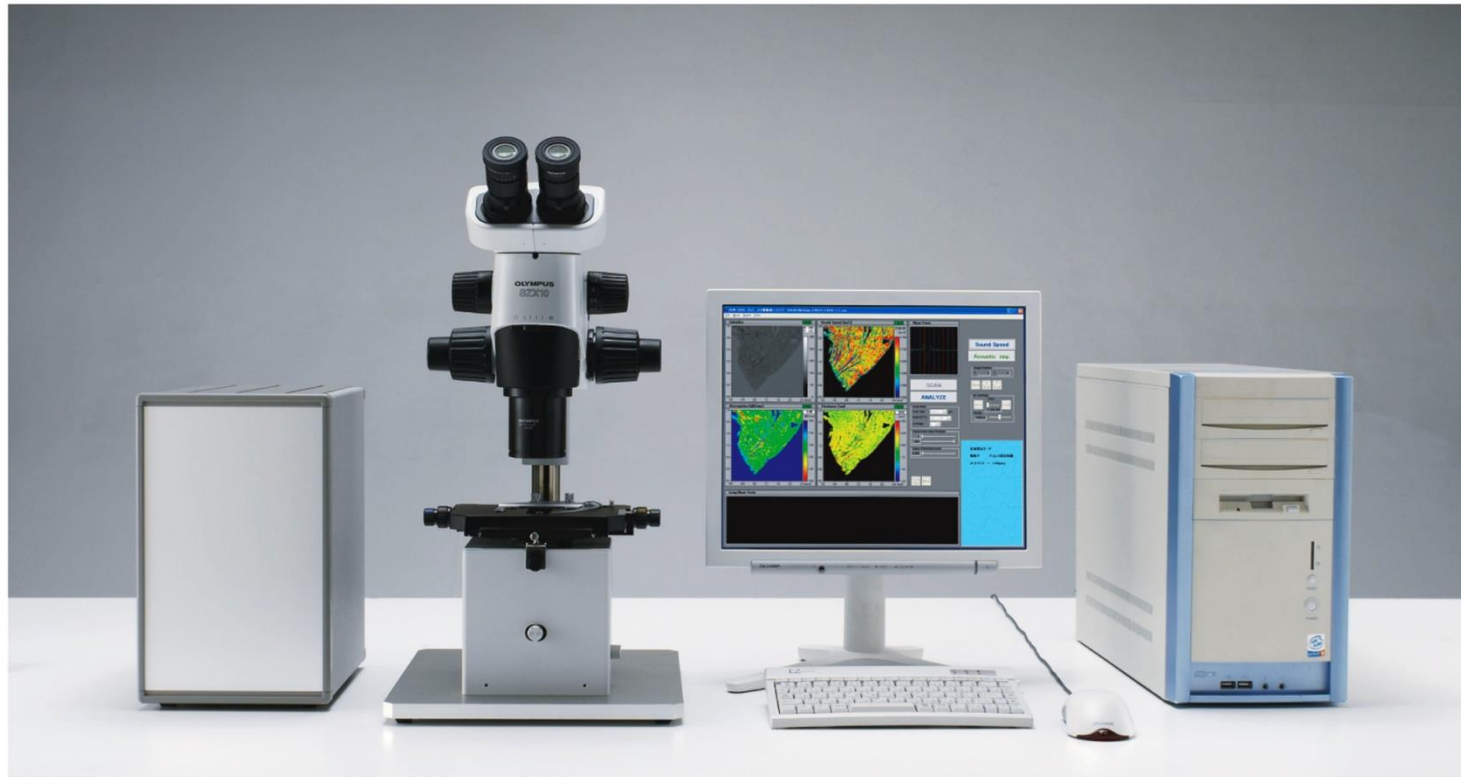


**1985 Burst Driven Type
Ultrasonic Microscope**



HONDA Electronics

AMS-50SI

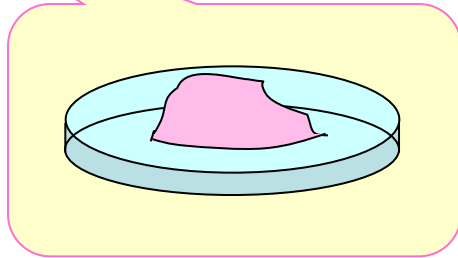


Summary

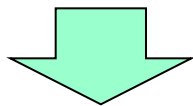
1. **Acoustic impedance microscope** was proposed.
2. No need to slice, stain. Non-contact.
3. Estimation error **by assuming vertical incidence** is significant if;
4. The error may be **compensated**.
5. Calibration by using **saline solution**.
6. **Cerebellar tissue** was observed.
7. **Cultured cells** were observed with a sufficient resolution.

What can we do next ?

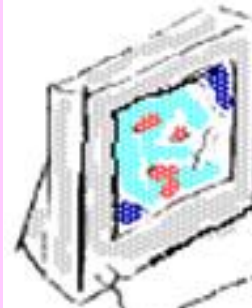
Direct probing



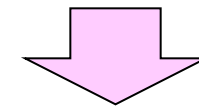
Non-sliced specimen



This presentation

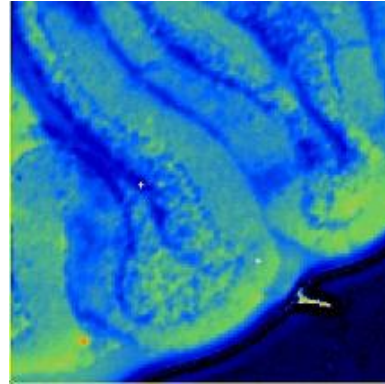
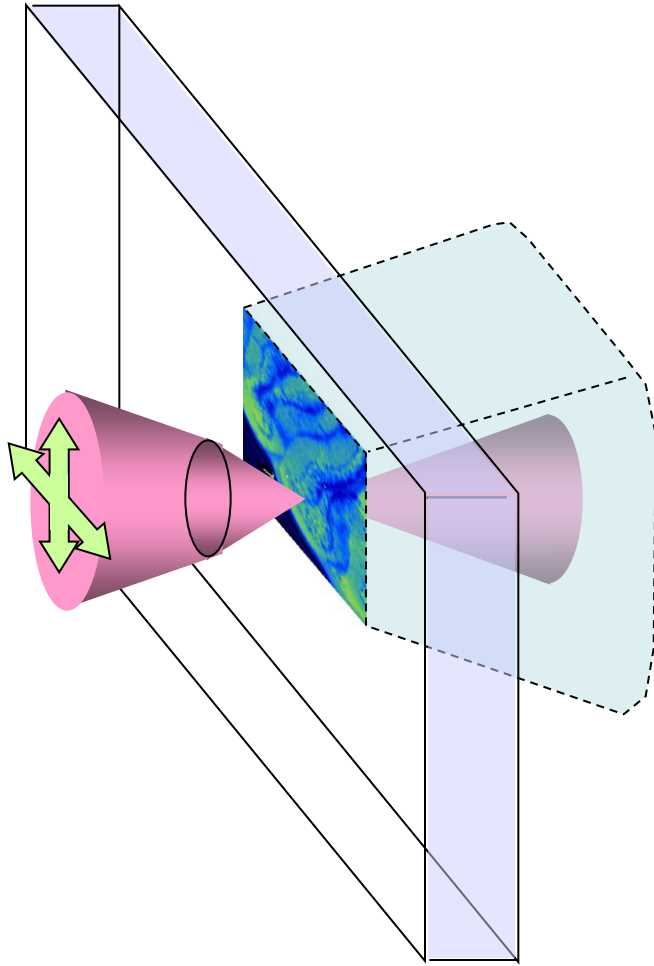


Direct probing



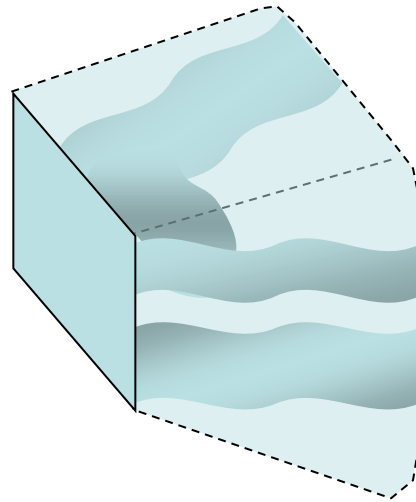
Future ?

A hybrid 2D 3D microscope



2D Profile of
Acoustic Impedance

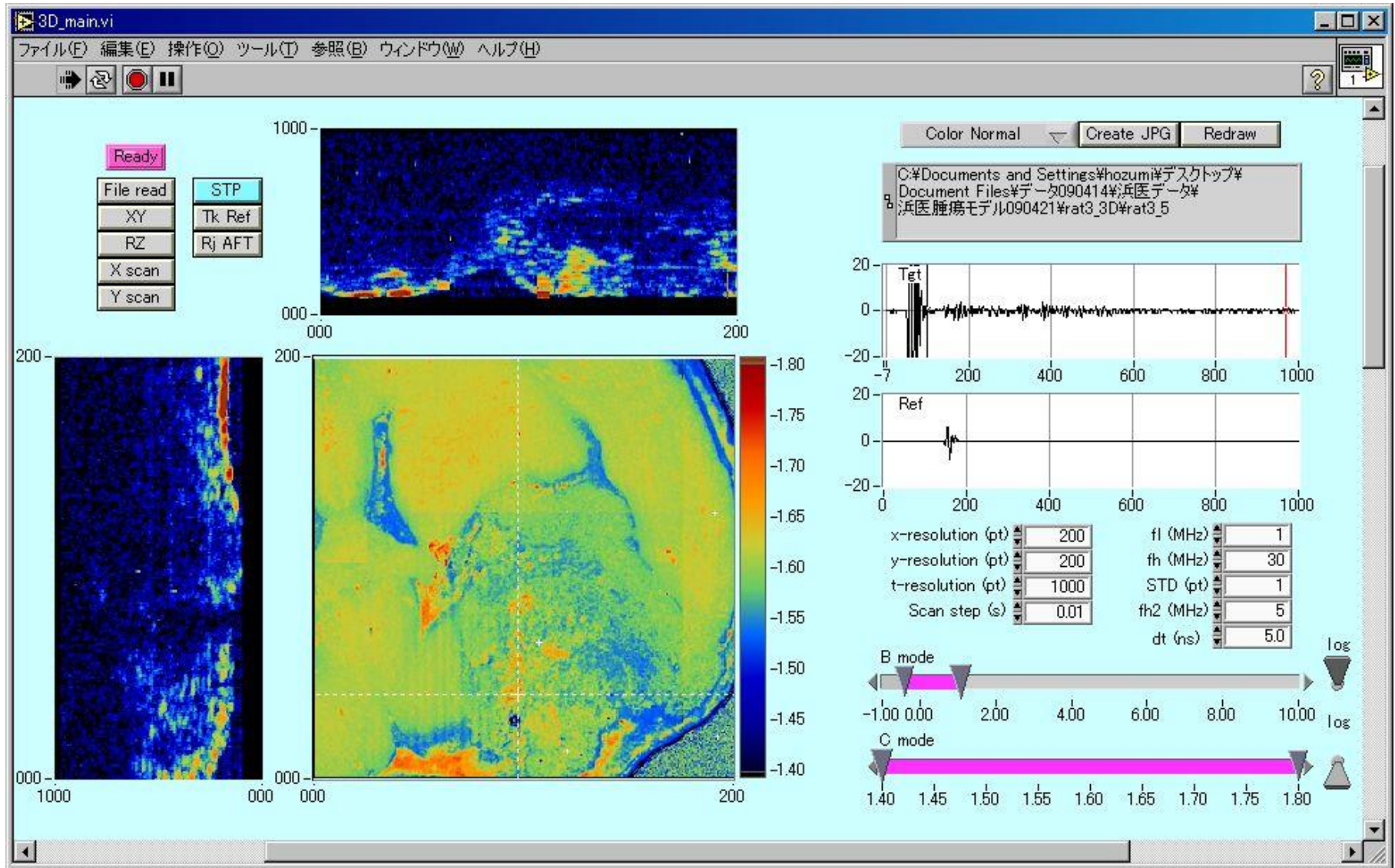
Quantitative



3D Profile by
Synthetic Aperture

Morphological

A hybrid 2D 3D microscope

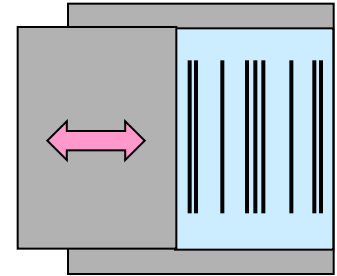


生体軟組織の縦波物性と横波物性。

縦波特性は体積弾性率 K で決まる。

$$c_p = \sqrt{(K + \frac{4}{3}G) / \rho},$$

$$Z_p = \rho c_p \quad K \gg G$$



気体・液体
・固体

横波特性はずり弾性率 G で決まる。

$$c_s = \sqrt{G / \rho},$$

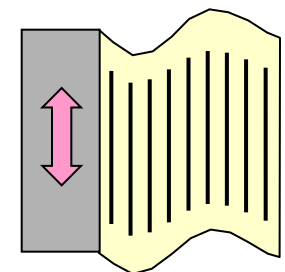
$$Z_s = \rho c_s$$

Z : 特性音響インピーダンス

c : 音速 ρ : 密度

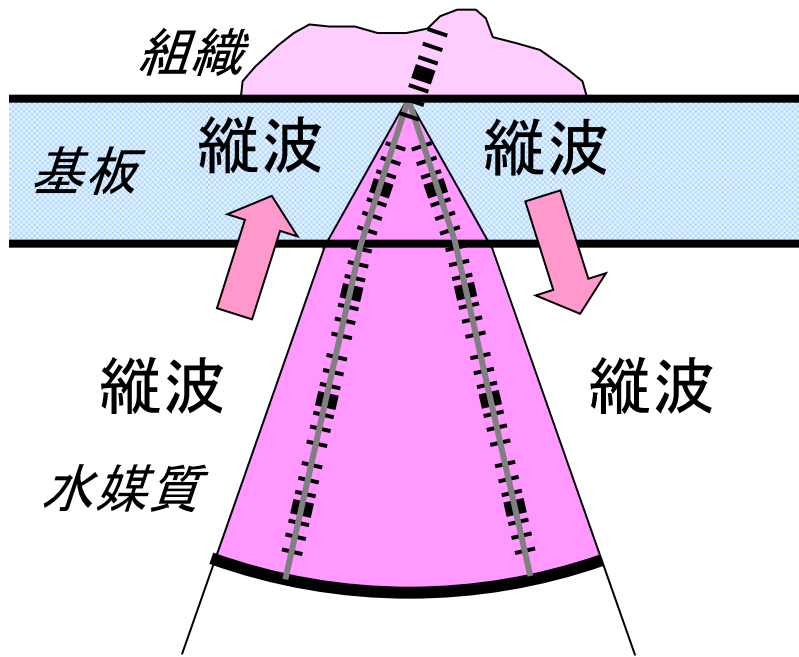
p : 縦波 (pressure wave)

s : 横波 (shear wave)

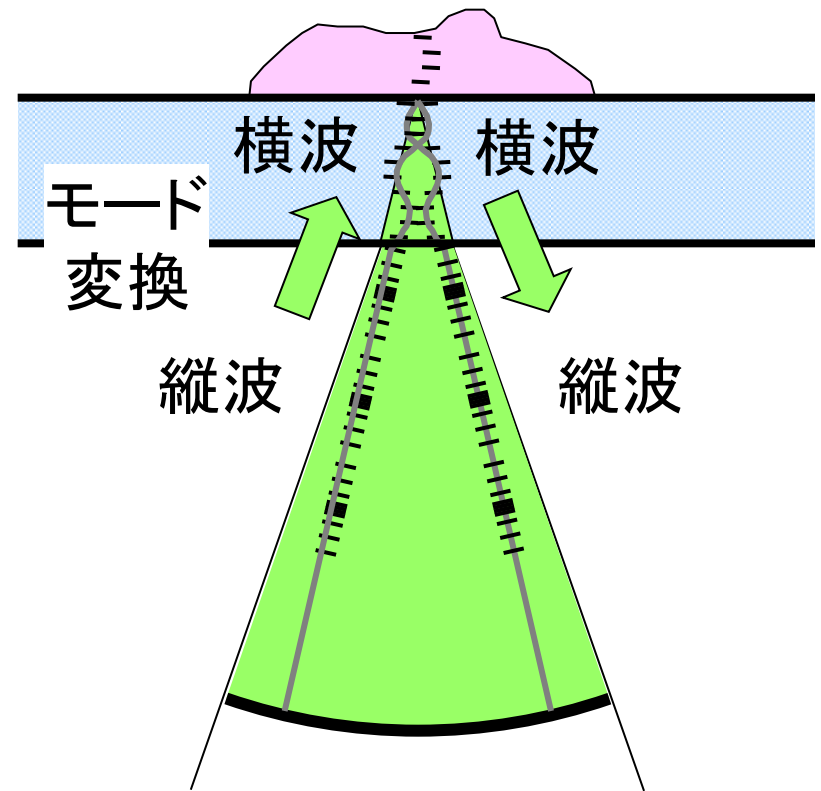


固体のみ

縦波と横波の出し方。

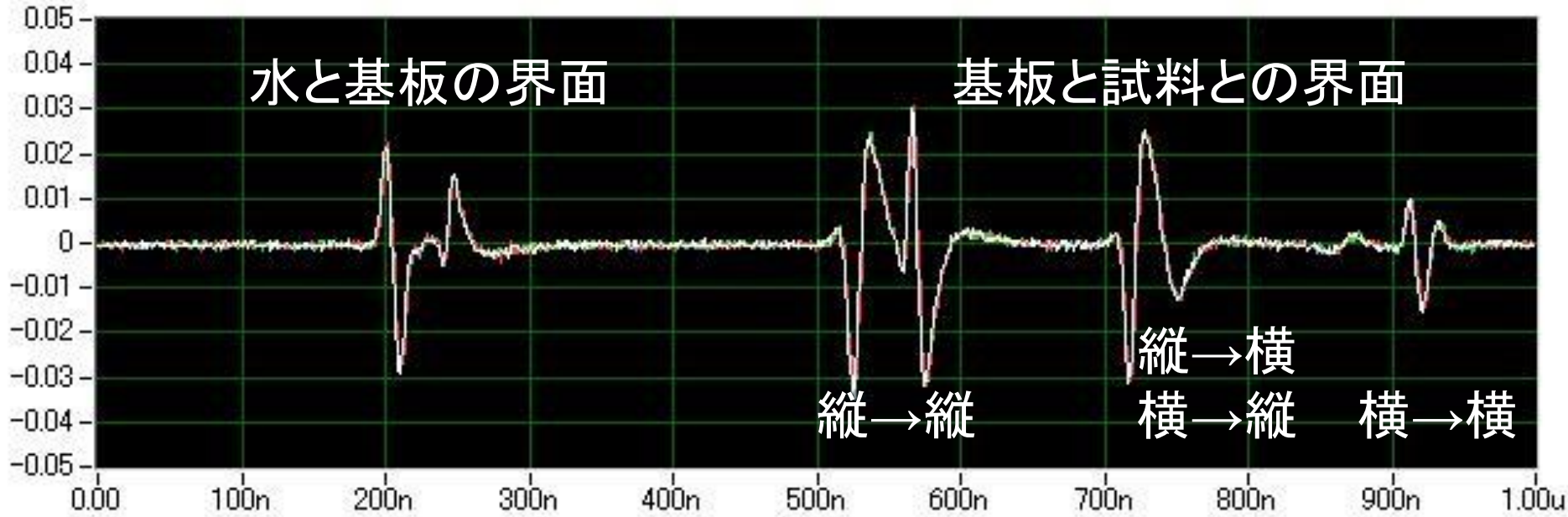


縦波



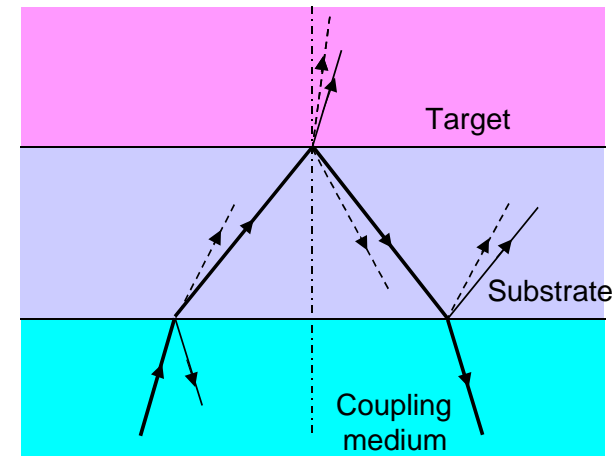
縦波

多くの反射波から横→横の反射を取出す。

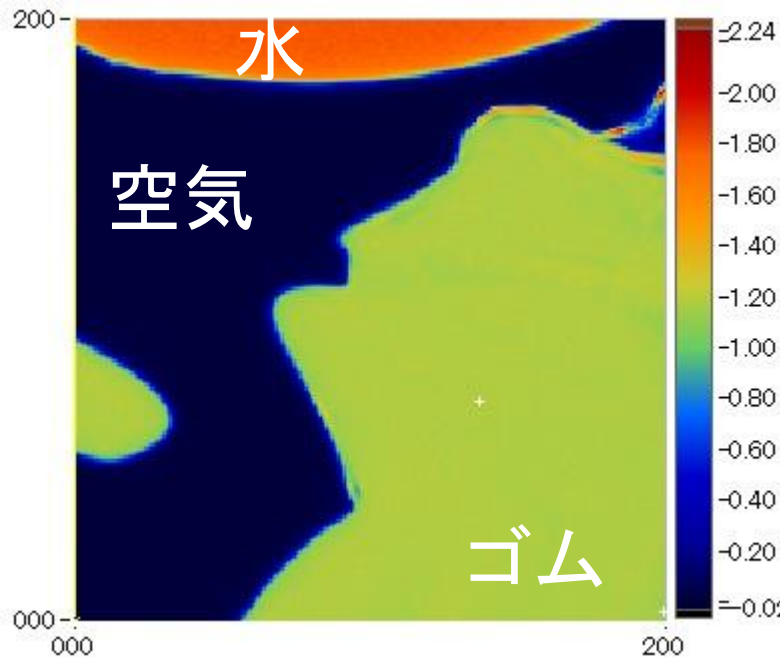


縦波入射→縦波反射と
横波入射→横波反射のモードが使える。

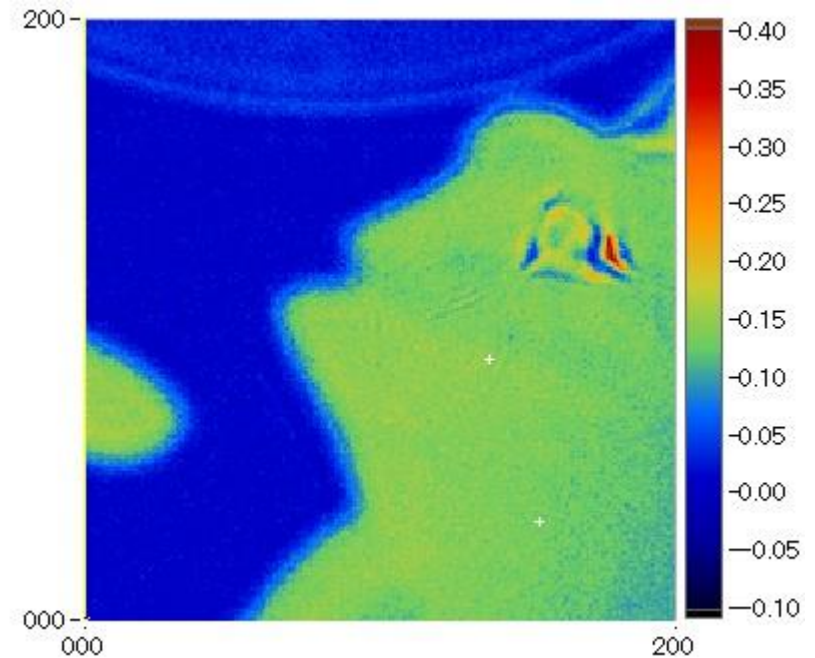
縦波入射→横波反射と
横波入射→縦波反射は集束しない。



空気とゴムと水を見た結果(音響インピーダンス)



縦波



横波

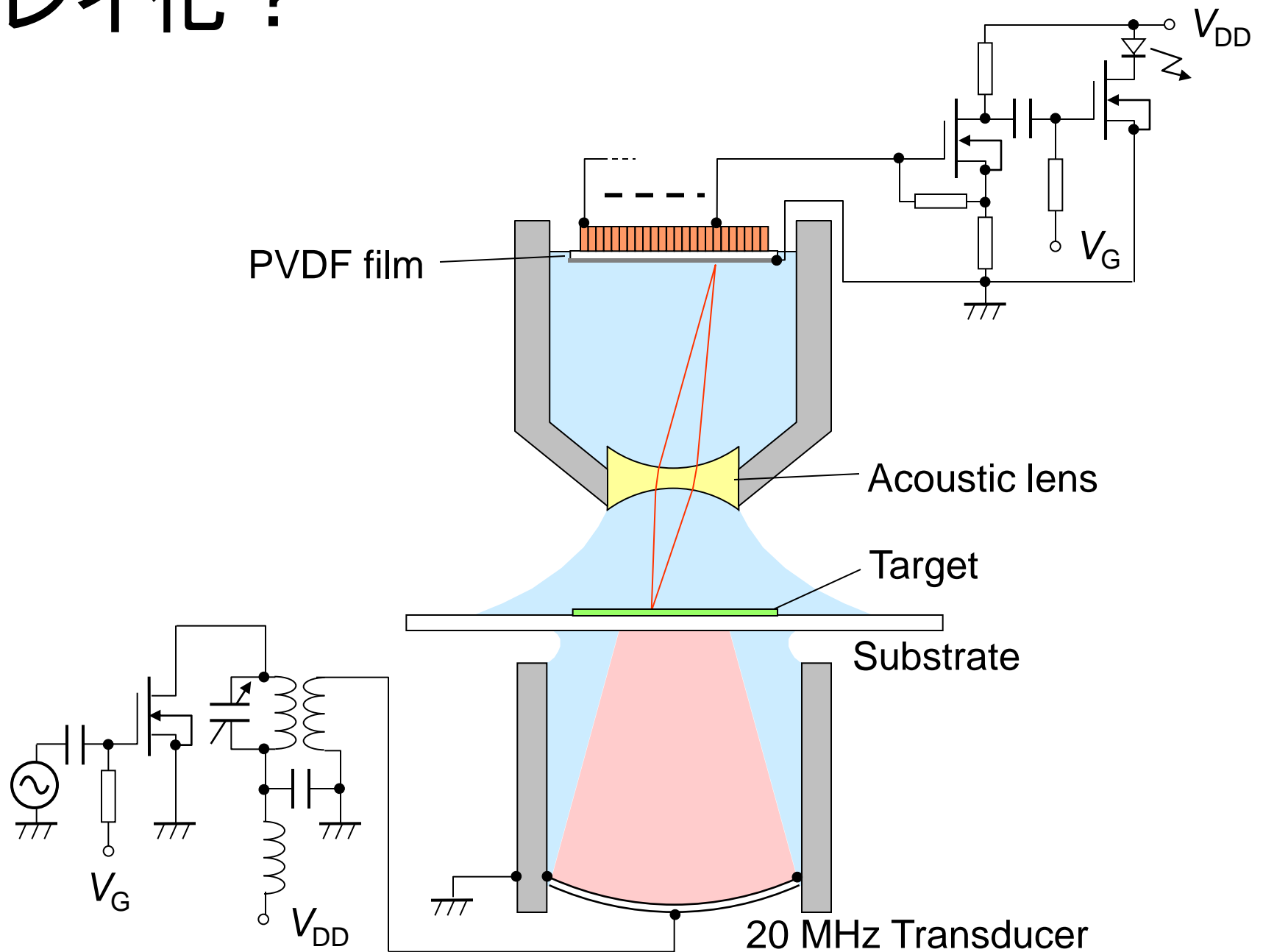
2 mm × 2 mm

音響インピーダンスと音速

縦波: 空気 < ゴム < 水 横波: 空気 = 水 < ゴム

横波で見ると、ゴムが最も硬くて水と空気は同じ程度。

アレイ化？



Thank you for your attention.